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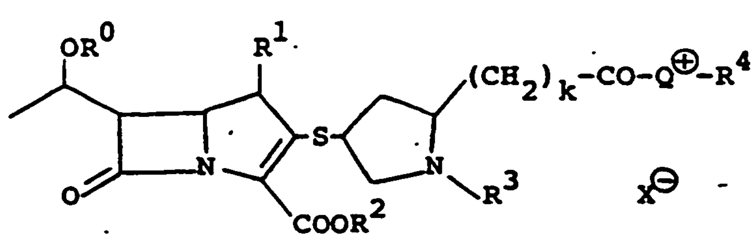
(54) Novel beta-lactam compounds and their production.

(57) A compound of the formula:



, which is us ful as an antimicrobial agent.

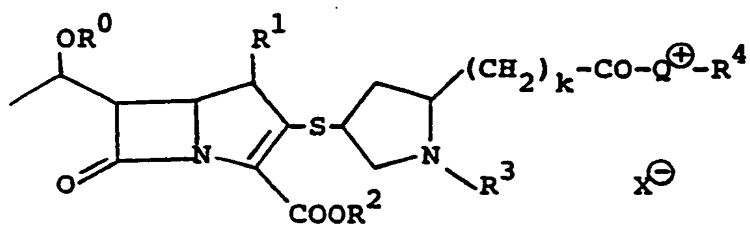
EP 0 442 497 A1

The present invention relates to β-lactam compounds and th ir production. More particularly, it relates to novel 3-pyrrolidinylthio-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylic acid compounds bearing a quaternary ammonium group on the pyrrolidine ring and th ir production.

There are known some β-lactam compounds having a carbapenem skeleton, which possess an excellent antimicrobial spectrum against a wide range of Gram-positive and Gram-negative bacteria. Among them, imipenem is already available on the market. Since, however, imipenem is sensitive to renal dehydropeptidase-I (DHP-I) in a living body and apt to be inactivated, it is normally used in combination with cylastatin for preventing the inactivation with DHP-I. Needless to say, it is clinically favorable that an antimicrobial agent exerts its antimicrobial activity without any auxiliary agent, and a great demand is present towards the development of a β-lactam compound which exerts its antimicrobial activity with resistance to DHP-I, i.e. saving the use of any auxiliary agent.

As the result of an extensive study, it has now been found that some 3-pyrrolidinylthio-1-azabicyclo-[3.2.0]hept-2-en-7-one-2-carboxylic acid compounds having a quaternary ammonium group on the pyrrolidine ring exerts a strong antimicrobial activity with sufficient resistance to DHP-I. The present invention is based on the above finding.

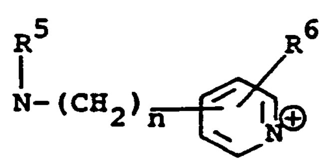
Accordingly, a basic object of the present invention is to provide a novel β-lactam compound of th formula:



(I)

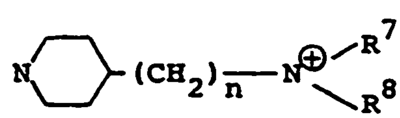
wherein R^0 is a hydrogen atom or a protective group for hydroxyl, R^1 is a lower alkyl group, R^2 is a protective group for carboxyl or a negative charge, R^3 is a hydrogen atom or a protective group for amino, R^4 is a lower alkyl group or a substituted lower alkyl group, k is an integer of 0 to 4, X is an acid residue or intramolecular COO when R^2 is the negative charge and $Q^{\oplus}$ is a quaternary nitrogen atom-containing group represented by either one of the formulas (1) to (4):

(1)



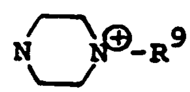
wherein R^5 is a hydrogen atom, a lower alkyl group or a 2-hydroxyethyl group, R^6 is a hydrogen atom or a lower alkyl group and n is an integer of 0 to 4;

(2)

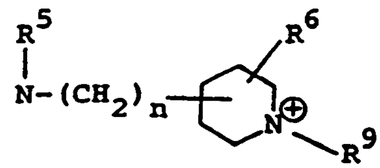


wherein R^7 and R^8 are each a lower alkyl group or may be combined together to form a lower alkylene group, or R^8 represents a substituted lower alkyl group and n is as defined ab ve;

(3)

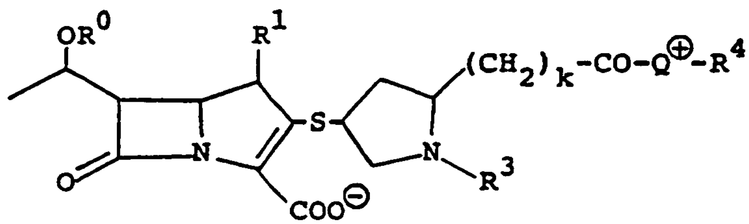


wherein R^9 is a lower alkyl group or a substituted lower alkyl group; or

(4) 

wherein R^5, R^6, R^9 and n are each as defined above.

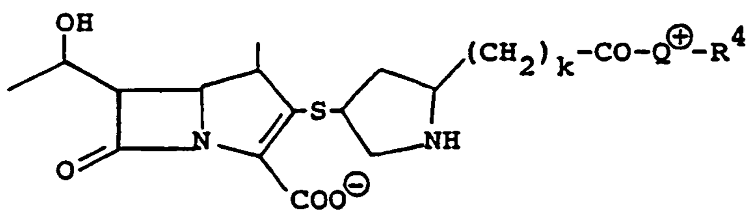
When R^2 is a negative charge and X is intra-molecular COO, the β-lactam compound (I) forms an intra-molecular quaternary salt, which is represented by the formula:



(I-a)

wherein R^0, R^1, R^3, R^4, k and $Q^{\oplus}$ are each as defined above.

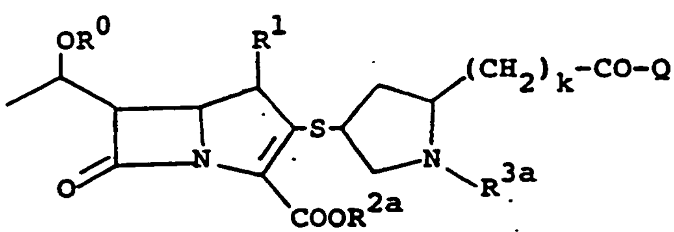
Among various β-lactam compounds which fall within the formula (I), the most preferred are those of the formula:



(I-b)

wherein R^4, k and $Q^{\oplus}$ are each as defined above.

According to the present invention, the β-lactam compound (I) can be produced by reacting a β-lactam compound of the formula:

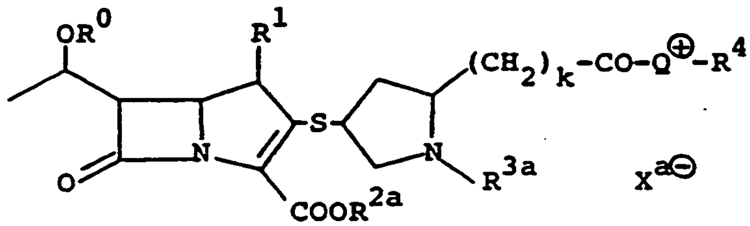


(II)

wherein R^0, R^1 and k are each as defined above, R^{2a} is a protective group for carboxyl, R^{3a} is a protectiv group for amino and Q is a tertiary nitrogen atom-containing group resulting from elimination of a positive charge from ither one of the groups (1) to (4) r pres nted by $Q^{\oplus}$ with a compound of the formula:

R^4-X^a (III)

wherein R^4 is as defined above and X^a is an acid residue to give a β-lactam compound of th formula:



(IV)

wherein R^0, R^1, R^{2a}, R^{3a}, R^4, k, $Q^{\bullet}$ and X^a are each as defined above, optionally followed by subjecting the β-lactam compound (IV) to elimination of the hydroxyl-protecting group represented by R^0, elimination of the carboxyl-protecting group represented by R^{2a} and/or elimination of the amino-protecting group represented by R^{3a}, thereby giving the β-lactam compound (I) wherein R^0 and R^3 are each a hydrogen atom and R^2 is a negative charge.

With respect to the definitions of the symbols as given above, the term "lower" is intended to mean a group normally having not more than 8 carbon atoms, preferably not more than 5 carbon atoms.

The protective group for hydroxyl (i.e. hydroxyl-protecting group) represented by R^0 and the protectiv group for amino (i.e. amino-protecting group) represented by R^3 or R^{3a} may be any group as conventionally used in the related art field. Preferred examples are C_1-C_5 alkoxycarbonyl (e.g. t-butyloxycarbonyl), halo-(C_1-C_5)alkoxycarbonyl (e.g. 2-iodoethyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl), C_3-C_7 alkenyloxycarbonyl (e.g. allyloxycarbonyl), ar(C_1-C_3)alkyloxycarbonyl such as phenyl(C_1-C_3)alkyloxycarbonyl (e.g. benzyloxycarbonyl) or substituted phenyl(C_1-C_3)alkyloxycarbonyl (e.g. p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl), and tri(C_1-C_5)alkylsilyl (e.g. trimethylsilyl, t-butyldimethylsilyl) groups.

The protective group for carboxyl (i.e. carboxyl-protective group) represented by R^2 or R^{2a} may be also any group as conventionally used. Preferred examples are straight or branched C_1-C_5 lower alkyl (e.g. methyl, ethyl, isopropyl, t-butyl), halo(C_1-C_5)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl), C_1-C_5 alkoxymethyl (e.g. methoxyethyl, ethoxymethyl, isobutoxymethyl), C_1-C_5 aliphatic acyloxymethyl (e.g. acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl), 1-(C_1-C_5)alkoxycarbonyloxyethyl (e.g. 1-ethoxycarbonyloxyethyl), ar(C_1-C_3)alkyl such as phenyl(C_1-C_3)alkyl (e.g. benzyl) or substituted phenyl(C_1-C_3)-alkyl (e.g. p-methoxybenzyl, o-nitrogenzyl, p-nitrobenzyl), C_3-C_7 alkenyl (e.g. allyl, 2-methylallyl, 3-methylallyl), benzhydryl and phthalidyl groups.

Examples of the lower alkyl group represented by R^1, R^4, R^5, R^6, R^7, R^8 or R^9 are C_1-C_5 alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl) groups. In case of the substituted lower alkyl group represented by R^4, R^8 or R^9, the substituent on the lower alkyl group may be, for instance, carboxyl, lower alkanoyl (e.g. acetyl, propionyl), carbamoyl, lower alkylaminocarbonyl (e.g. methylaminocarbonyl), di(lower)-alkylaminocarbonyl (e.g. dimethylaminocarbonyl), cyano, lower alkoxy (e.g. methoxy, ethoxy), hydroxyl, and phenyl proups. Thus, examples of the substituted lower alkyl group are C_1-C_7 alkyl substituted with one or more substitutents as exemplified above, specifically carboxymethyl, acetylmethyl, propionylmethyl, carbamoylmethyl, N-methylaminocarbonylmethyl, N,N-dimethylaminocarbonylmethyl, 2-cyanoethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-carboxyethyl, 2-hydroxyethyl, 2-carbamoylethyl, 2-N-methylaminocarbonylethyl, 2-N,N-dimethylaminocarbonylethyl, 3-carboxypropyl, 4-hydroxybutyl, 5-hydroxypentyl and benzyl groups.

When R^7 and R^8 are combined together to make a lower alkylene group, they form a 3- to 7-membered ring together with the nitrogen atom to which they are attached, and examples of the 3- to 7-membered ring are aziridine, azetidine, pyrrolidine and piperidine groups.

Examples of the acid residue represented by X or X^a are an inorganic acid residue (e.g. chlorine, bromine, fluorine, iodine) or an organic acid residue (e.g. benzenesulfonyloxy, p-toluenesulfonyloxy, methanesulfonyloxy, trifluoromethanesulfonyloxy).

The β-lactam compound (I) may be either in a free form or in a salt (preferably non-toxic salt) form. Examples of the salt are inorganic base salts (e.g. sodium, potassium, calcium, magnesium, ammonium), organic base salts (e.g. triethylammonium, pyridinium, diosopropylammonium), inorganic acid addition salts (e.g. hydrochloride, sulfate, phosphate), and organic acid addition salts (e.g. formate, acetate, methanesulfonate, benzenesulfonat).

Production of the β-lactam compound (I) will be hereinafter explained in details.

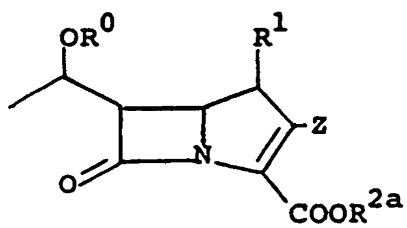
The quaternarization of th β-lactam compound (II) may be performed by a per s conventional procedure, for instance, by reacting the β-lactam compound (II) with th compound (III) in an inert solvent chosen from water, ketones (e.g. acetone, methylethylketone), thers (e.g. tetrahydrofuran, dioxane), acetonitrile and halogenated hydrocarbons (e.g. dichloromethane, dichloroethane, chloroform), or their

mixtures. There is no limitation on th reaction temperature, but th reaction is normally effected at a temperature of -40 to 60°C. Upon termination of th reaction, th objectiv product is isolated from th reaction mixture by a per se conventional procedure.

The thus obtained product, i.e. the β-lactam compound (IV), is optionally subjected to elimination of the hydroxyl-protecting group represented by R^0, elimination of the carboxyl-protecting group represented by R^{2a} and/or elimination of the amino-protecting group represented by R^{3a} to give the β-lactam compound (I) wherein at least one of R^0 and R^3 is a hydrogen atom and R^2 is a negative charge.

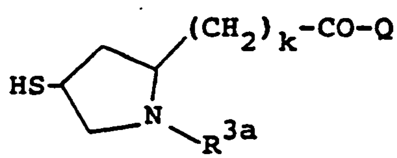
The elimination may be effected independently or concurrently by a per se conventional procedure such as treatment with an acid, a base or a reducing agent (T.W.Greene: Protective Groups in Organic Synthesis, J. Wiley & Sons Inc., 1981). As the acid, there are exemplified trifluoroacetic acid, formic acid, boron trifluoride and aluminium chloride. As the base, there are exemplified alkali metal carbonate (e.g. sodium carbonate, potassium carbonate), alkali metal sulfate (e.g. sodium sulfate, potassium sulfate) and tetrafluorobutylammonium. When the elimination is conducted through reduction, there may be adopted any procedure using zinc and acetic acid, hydrogen and palladium-carbon or platinum. The elimination with tetrakistriphenylphosphine palladium is also available. Any particular limitation is not present on the solvent to be used, and it may be chosen from water, alcohols (e.g. methanol, ethanol), ethers (e.g. tetrahydrofuran, dioxane) and aliphatic acids (e.g. acetic acid). The reaction temperature may be appropiately decided so as to control or accelerate the proceeding of the reaction, and a preferred temperture is normally from -30 to 40°C. The reaction product may be separated from the reaction mixture by a per se conventional procedure. For instance, the reaction mixture is neutralized and chromatographed on an adsorptive resin, followed by elution and lyophilization.

The β-lactam compound (II) as the starting compound is obtainable by reacting a β-lactam compound of the formula:



(V)

wherein R^0, R^1 and R^{2a} are each as defined above and Z is a reactive ester on hydroxyl with a mercaptan compound of the formula:



(VI)

wherein R^{3a}, k and Q are each as defined above in an inert solvent in the presence of a base.

The β-lactam compound (V) is known (cf. Heterocycles, Vol. 21, p. 29-40, 1984), and its reactive ester on hydroxyl represented by Z may be chosen, for instance, from arylsulfonates such as benzenesulfonat s and substituted benzenesulfonates (e.g. p-toluenesulfonate, p-nitrobenzenesulfonate, p-bromobenzenesulfonate), C_1-C_5 alkanesulfonates (e.g. methanesulfonate, ethanesulfonate), halo(C_1-C_5)alkanesulfonates (e.g. trifluoromethanesulfonate), diarylphosphates (e.g. diphenylphosphate) and halides (e.g. chloride, bromide, iodide). Of these, p-toluenesulfuonate, methanesulfonate and diphenylphosphate are prefered.

The mercaptan compound (VI), which may be produced from trans-4-hydroxy-L-proline or cis-4-hydroxy-D-proline by a known method (cf. U.S. Patent Nos. 4,943,569 and 4,962,103), is usually employed in an excessive amount, particularly in a 1 to 2 equivalent amount to the β-lactam compound (V) so that th reaction with the β-lactam compound (V) proceeds sufficiently.

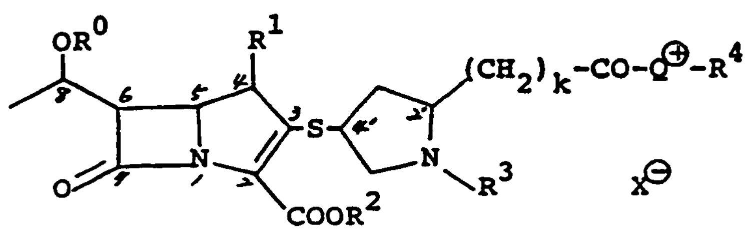
Examples of the inert solvent are dioxane, tetrahydrofuran, dimethylsulfoxide, acetonitrile and hexamethylphosphoramide. As the base, there may be used an inorganic base (e.g. sodium carbonat , potassium carbonate, sodium hydride, potassium hydride, potassium t-butoxide), an organic bas (e.g. pyridine, dimethylaminopyridine, triethylamine, diisopropylethylamine and 1,8-diazabicyclo[5.4.0]-undec-7-

ene (DBU), among which preferred ar diisopropylethylamine and DBU. Th base is used in such an amount as can assur th smooth proceeding of the reaction, normally in a 1 to 3 equimolar amount to the mercaptan compound (VI).

The reaction is normally carried out at a temperture of from -78 to 60 °C, preferably from -40 to 40 °C.

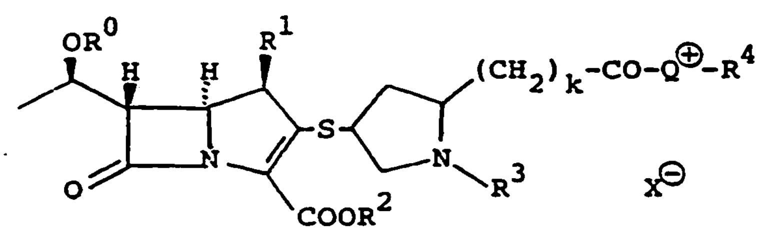
Upon termination of the reaction, the reaction mixture may be subjected to post-treatment in a per se conventional procedure so as to obtain the objective β-lactam compound (II), if necessary, followed by purification.

The β-lactam compound (I) of the invention includes asymmetric carbon atoms at the 4-, 5-, 6- and 8-positions in the carbapenem skeleton as shown in the following formula and has optical and steric isomers due to those asymmetric arbon atoms:



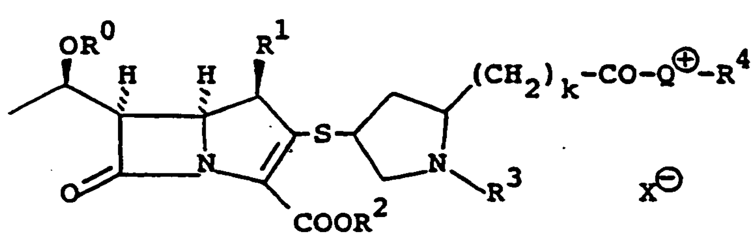
(I')

wherein R^0, R^1, R^2, R^3, R^4, k and $Q^{\bullet}$ and $X^{\ominus}$ are each as defined above. While all these optical and steric isomers and their mixtures fall within the scope of the invention, preferred are those having an S-configuration at the 5-position, i.e. (5S,6S) or (5S,6R), those having an R-configuration at the 8-position and those having an R configuration at the 4-position. More preferred are those having a (4R,5S,6S,8R) configuration as represented by the formula (I'-a) or a (4R,5S,6R,8R) configuraton as represented by the formula (I'-b):



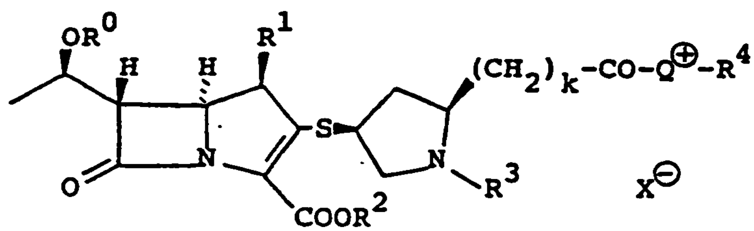
(I'-a)

and



(I'-b)

wherein R^0, R^1, R^2, R^3, R^4, k, $Q^{\bullet}$ and $X^{\ominus}$ are each as defined above. The most preferred are those of the formula (I'-c):



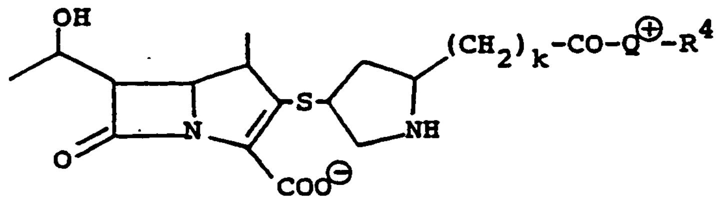
(I'-c)

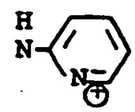
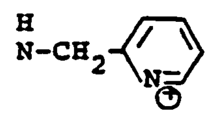
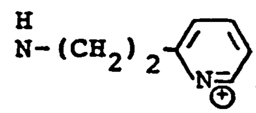
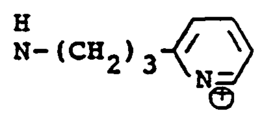
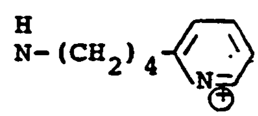
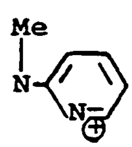
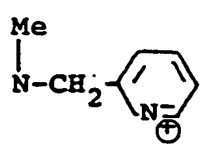
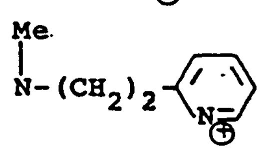
wherein R^0, R^1, R^2, R^3, R^4, k, $Q^{\oplus}$ and $X^{\ominus}$ are each as defined above.

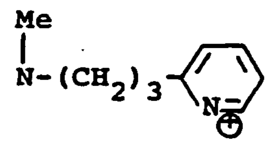
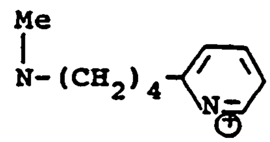
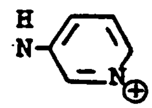
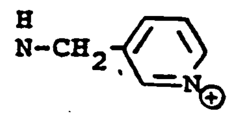
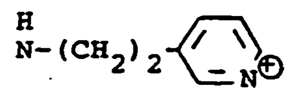
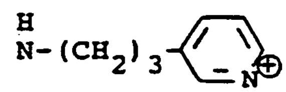
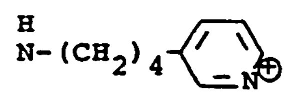
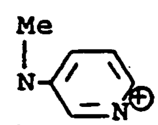
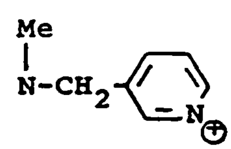
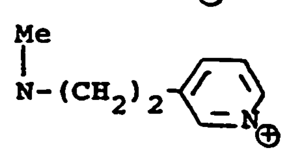
Production of the specific isomers as above stated can be achieved by the use of the corresponding isomers of the β-lactam compound (V) and the mercaptan compound (VI).

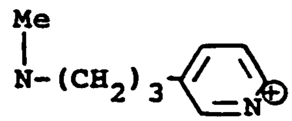
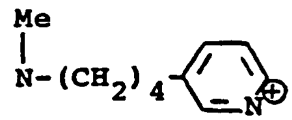
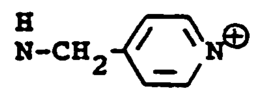
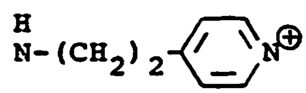
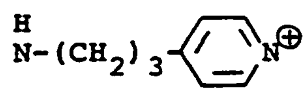
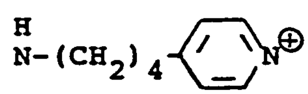
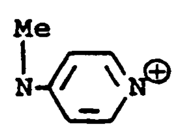
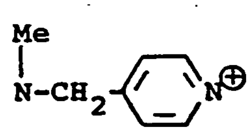
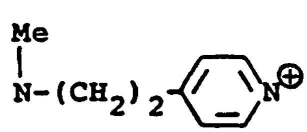
Typical examples of the β-lactam compound (I) wherein R^0 and R^3 are each a hydrogen atom, R^1 is a methyl group and R^2 is a negative charge are shown in Table 1, in which Me and Ph indicate respectively methyl and phenyl.

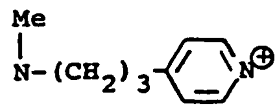
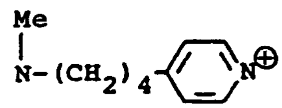
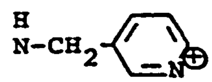
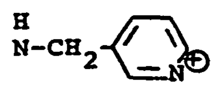
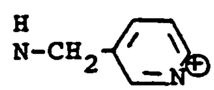
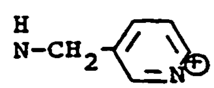
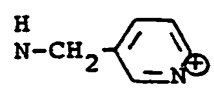
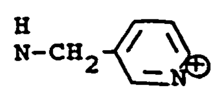
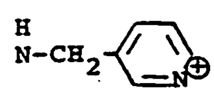
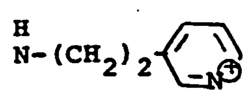
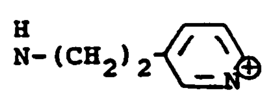
Table 1

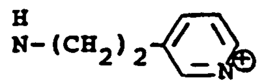
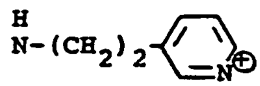
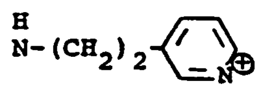
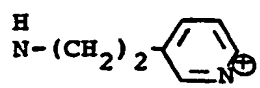
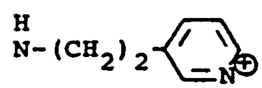
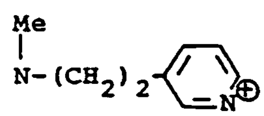
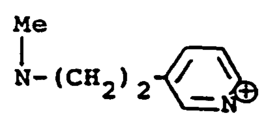
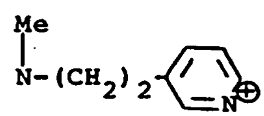
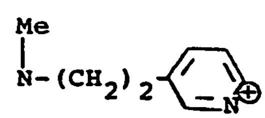
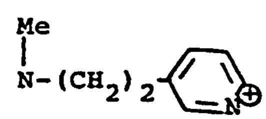
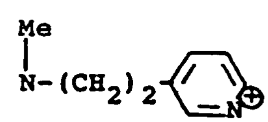


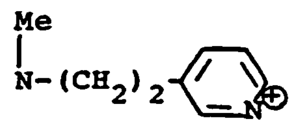
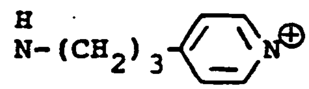
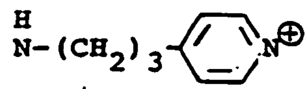
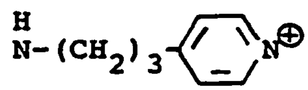
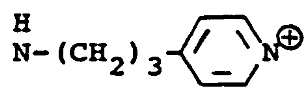
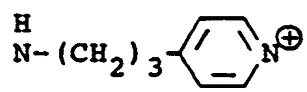
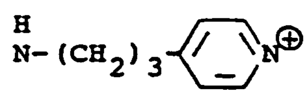
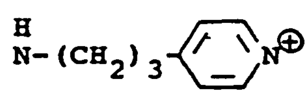
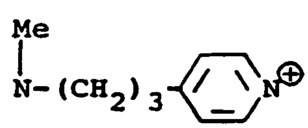
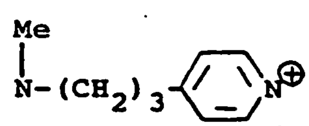
Compound No.	k	$Q^{\oplus}$	R^4
1	0		Me
2	0		Me
3	0		Me
4	0		Me
5	0		Me
6	0		Me
7	0		Me
8	0		Me

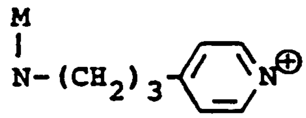
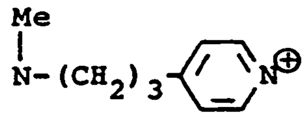
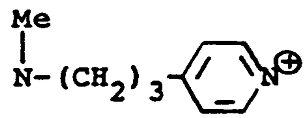
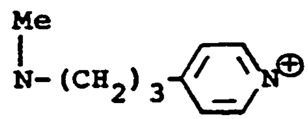
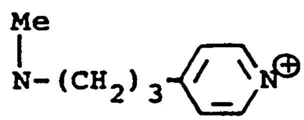
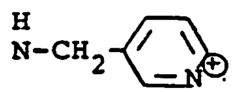
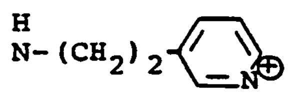
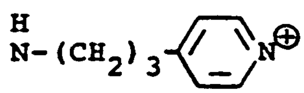
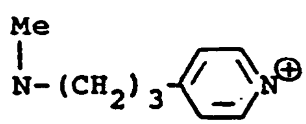
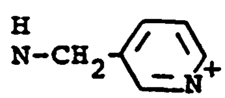
Compound No.	k	$Q^{\oplus}$	R^4
9	0		Me
10	0		Me
11	0		Me
12	0		Me
13	0		Me
14	0		Me
15	0		Me
16	0		Me
17	0		Me
18	0		Me

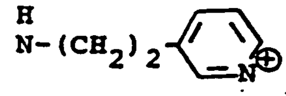
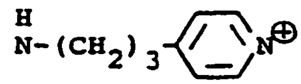
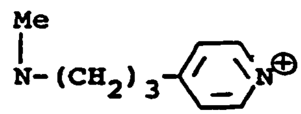
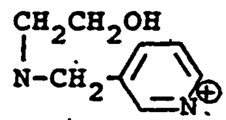
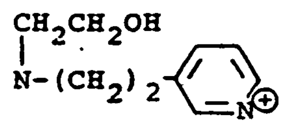
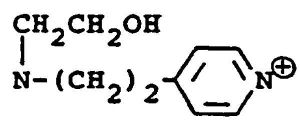
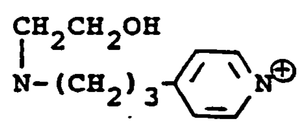
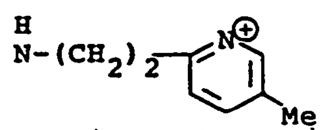
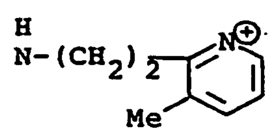
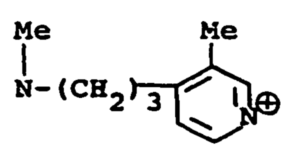
Compound No.	k	$Q^{\oplus}$	R^4
19	0		Me
20	0		Me
21	0		Me
22	0		Me
23	0		Me
24	0		Me
25	0		Me
26	0		Me
27	0		Me
28	0		Me

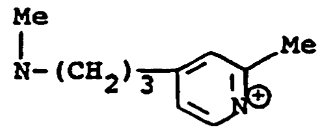
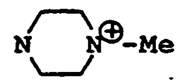
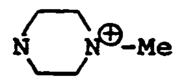
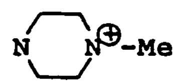
Compound No.	k	$Q^{\oplus}$	R^4
29	0		Me
30	0		Me
31	0		CH_2Ph
32	0		CH_2COOH
33	0		CH_2CH_2OH
34	0		CH_2CONH_2
35	0		$CH_2CONH(Me)$
36	0		$CH_2CON(Me)$-Me
37	0		$CH_2CH_2CON(Me)$-Me
38	0		CH_2Ph
39	0		CH_2COOH

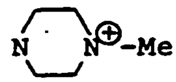
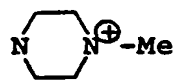
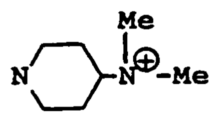
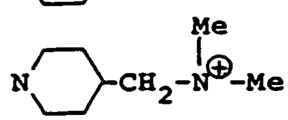
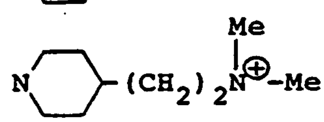
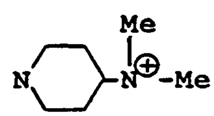
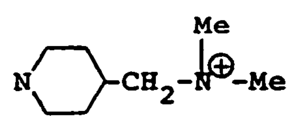
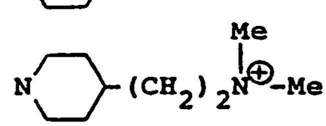
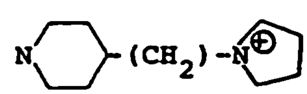
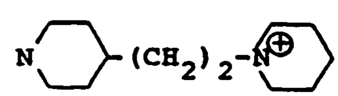
Compound N .	k	$Q^{\oplus}$	R^4
40	0		CH_2CH_2OH
41	0		CH_2CONH_2
42	0		$CH_2CON(Me)H$
43	0		$CH_2CON(Me)\text{-}Me$
44	0		$CH_2CH_2CON(Me)\text{-}Me$
45	0		$PhCH_2$
46	0		CH_2COOH
47	0		CH_2CH_2OH
48	0		CH_2CONH_2
49	0		$CH_2CON(Me)H$
50	0		$CH_2CON(Me)\text{-}Me$

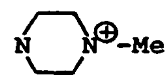
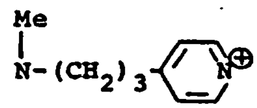
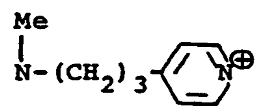
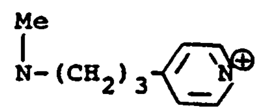
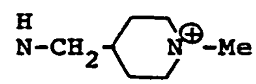
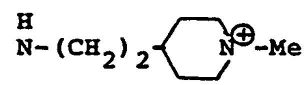
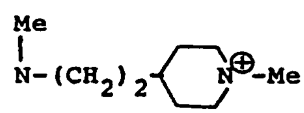
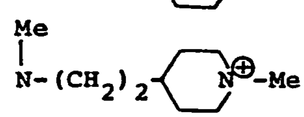
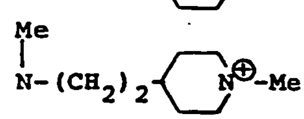
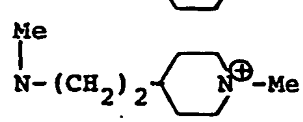
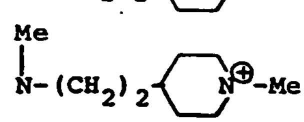
Compound No.	k	$Q^{\oplus}$	R^4
51	0		$CH_2CH_2CON(Me)$-Me
52	0		CH_2Ph
53	0		CH_2COOH
54	0		CH_2CH_2OH
55	0		CH_2CONH_2
56	0		$CH_2CON(Me)H$
57	0		$CH_2CON(Me)$-Me
58	0		$CH_2CH_2CON(Me)$-Me
59	0		CH_2Ph
60	0		CH_2COOH

Compound No.	k	$Q^{\oplus}$	R^4
61	0		CH_2CH_2OH
62	0		CH_2CONH_2
63	0		$CH_2CON(Me)H$
64	0		$CH_2CON(Me)-Me$
65	0		$CH_2CH_2CON(Me)-Me$
66	1		Me
67	1		Me
68	1		Me
69	1		Me
70	2		Me

Compound No.	k	$Q^{\oplus}$	R^4
71	2		Me
72	2		Me
73	2		Me
74	0		Me
75	0		Me
76	0		Me
77	0		Me
78	0		Me
79	0		Me
80	0		Me

Compound No.	k	$Q^{\oplus}$	R^4
81	0		Me
82	0		Me
83	0		CH_2Ph
84	0		CH_2COOH
85	0		CH_2CH_2OH
86	0		CH_2CONH_2
87	0		$CH_2CON(Me)H$
88	0		$CH_2CON(Me)-Me$
89	0		$CH_2CH_2CON(Me)-Me$
90	1		Me
91	1		CH_2Ph
92	1		CH_2COOH
93	1		CH_2CH_2OH

Compound No.	k	$Q^{\oplus}$	R^4
94	1		CH_2CONH_2
95	1		$CH_2CO\overset{Me}{\overset{\mid}{N}}H$
96	1		$CH_2CO\overset{Me}{\overset{\mid}{N}}\text{-}Me$
97	1		$CH_2CH_2CO\overset{Me}{\overset{\mid}{N}}\text{-}Me$
98	0		Me
99	0		Me
100	0		Me
101	1		Me
102	1		Me
103	1		Me
104	0		Me
105	0		Me

Compound No.	k	$Q^{\oplus}$	R^4
106	0		CH_2CH_2CN
107	0		CH_2CH_2OMe
108	0		CH_2CO-Me
109	0		CH_2CH_2CN
110	0		CH_2CH_2OMe
111	0		CH_2CO-Me
112	0		Me
113	0		Me
114	0		Me
115	0		CH_2COOH
116	0		CH_2CH_2OH
117	0		CH_2CONH_2
118	1		CH_2CO-Me

The β-lactam compounds as exemplified in Table 1 have their optical and steric isomers, and all of them are included within the scope of the present invention.

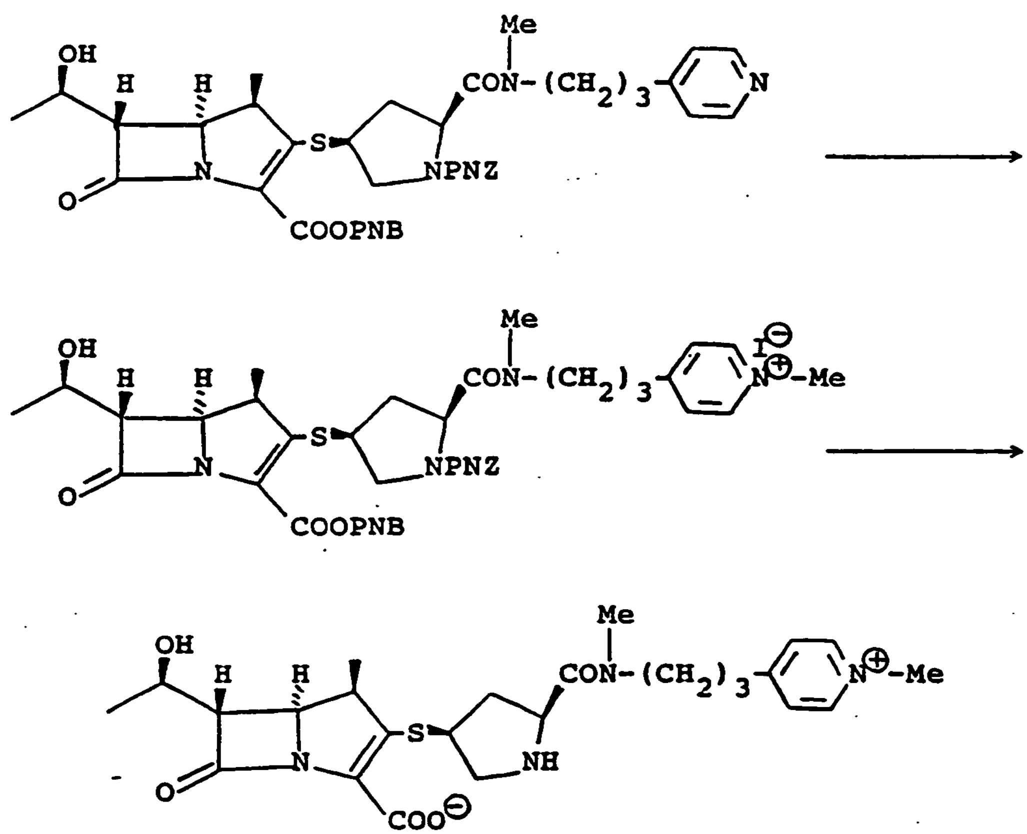
The β-lactam compounds (I) according to the invention are characteristic in having a 2-substituted pyrrolidin-4-ylthio group introduced with a quaternary ammonium group at the 3-position and a low r alkyl group at the 4-position in the carbapenem skeleton. Due to such characteristic structure, the β-lactam

compounds (I) xert an excellent antimicrobial activity against Gram-positiv and Gram-negativ bacteria including Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Serratia marcescens and Pseudomonas aeruginosa. It is notabl that while conventional carbap nem compounds such as imipen m are generally unstable in a living body, especially sensitive to renal DHP-I, the β-lactam compounds (I), particularly those wherein R^1 is a methyl group in the R-configuration, are in general significantly resistant to renal DHP-I. It is also notable that the half life time ($T\frac{1}{2}$) of the β-lactam compounds (I) in a living body is generally longer than that of conventional carbapenem compounds such as imipenem. The β-lactam compounds (I) are thus useful as antimicrobial drugs or intermediates in the synthesis of such antimicrobial drugs.

For the practical usage of the β-lactam compounds (I) as antimicrobial drugs, they may be formulated into conventional preparation forms together with excipients or additives such as carriers, diluents, binders and stabilizers and administered in various modes, of which examples are oral administration in the form of tablets, capsules, dispersants and syrups, non-oral administration in the form of injection through v in, muscle or rectum. When they are applied in injection forms, the preparations may additionally includ buffering agents, solubilizing agents and isotonic agents. The daily dosage may vary depending upon the state of disease, the age and body weight of patients, the administration mode and time, and the normal daily dosage to a human adult is between about 100 to 3000 mg, optinally divided in one to several times per day. If necessary, the dosage may be increased or decreased appropriately.

Practical and presently preferred embodiments of the invention are illustratively shown in the following Examples, which are not intended to limit the scope of the invention thereto. Further, the abbreviations used therein show the following meanings: PNZ, p-nitrobenzyloxycarbonyl; PNB, p-nitrobenzyl; Ph, phenyl; Ac, acetyl; TBDMS, t-butyldimethylsilyl; Me, methyl.

Example 1

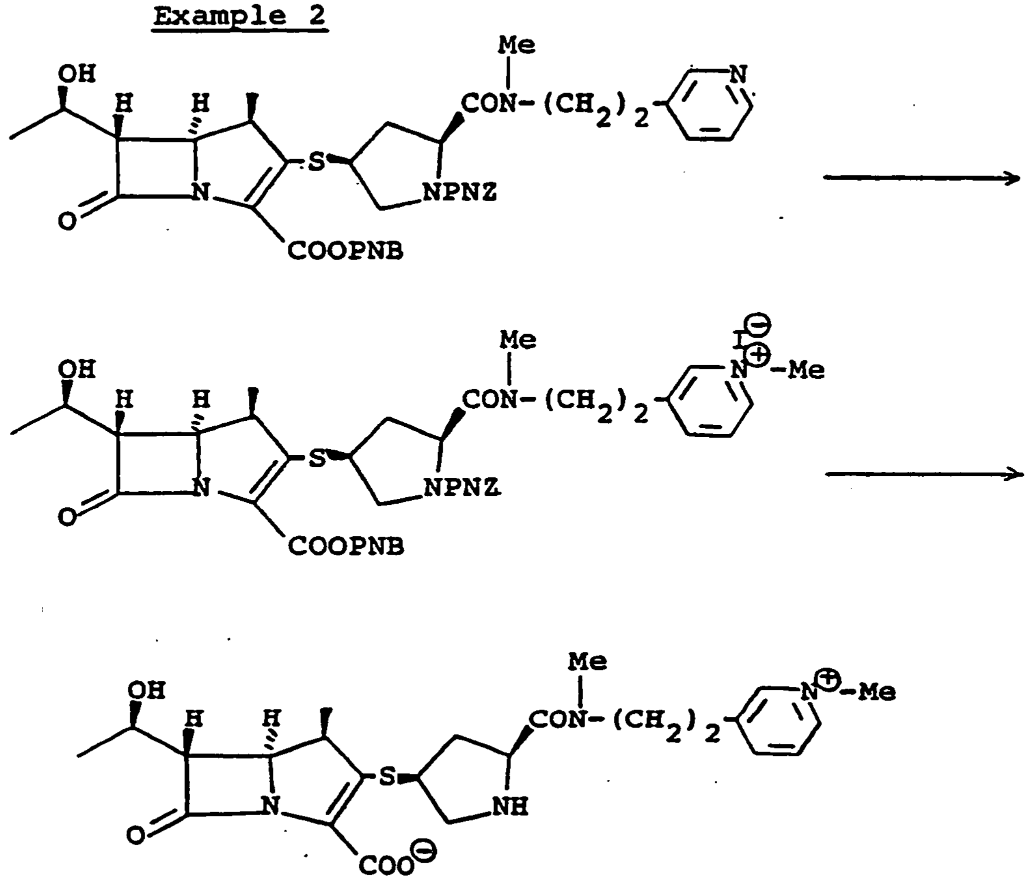


To a solution of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(3-(4-pyridyl)propyl)-methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (100 mg) in acetone (2.0 ml), methyl iodide (1.14 g) was added, and the resultant mixture was

stirred at room temperature for 20 hours, followed by removal of the solvent under reduced pressure. The residue was dissolved in tetrahydrofuran (5.0 ml) and 0.1M phosphate buffer (pH, 7.0; 5.0 ml), and 10 % palladium-carbon (150 mg) was added thereto. Catalytic reduction was performed at room temperature for 1.5 hours under atmospheric pressure of hydrogen. The catalyst was removed by filtration, and the filtrate was washed with dichloromethane three times. After removal of the solvent from the washed filtrate under reduced pressure, the residue was purified by polymer chromatography (CHP-20P) using 2 % aqueous tetrahydrofuran as an eluent. The eluted fractions were collected and freeze-dried to give (4R,5S,6S,8R,2'S,4'S)-3-[2-((3-(1-methylpyridinium-4-yl)propyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

UV_{max} nm (H_2O):	257, 263 (sh), 298;
IR_{max} cm^{-1} (KBr):	3400, 1737, 1682, 1367;
NMR δ (D_2O):	1.18 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.6 Hz), 3.04 (3H, s), 4.20 (3H, s), 7.87 (2H, d, J = 6.6 Hz), 8.60 (2H, d, J = 6.6 Hz).

Example 2

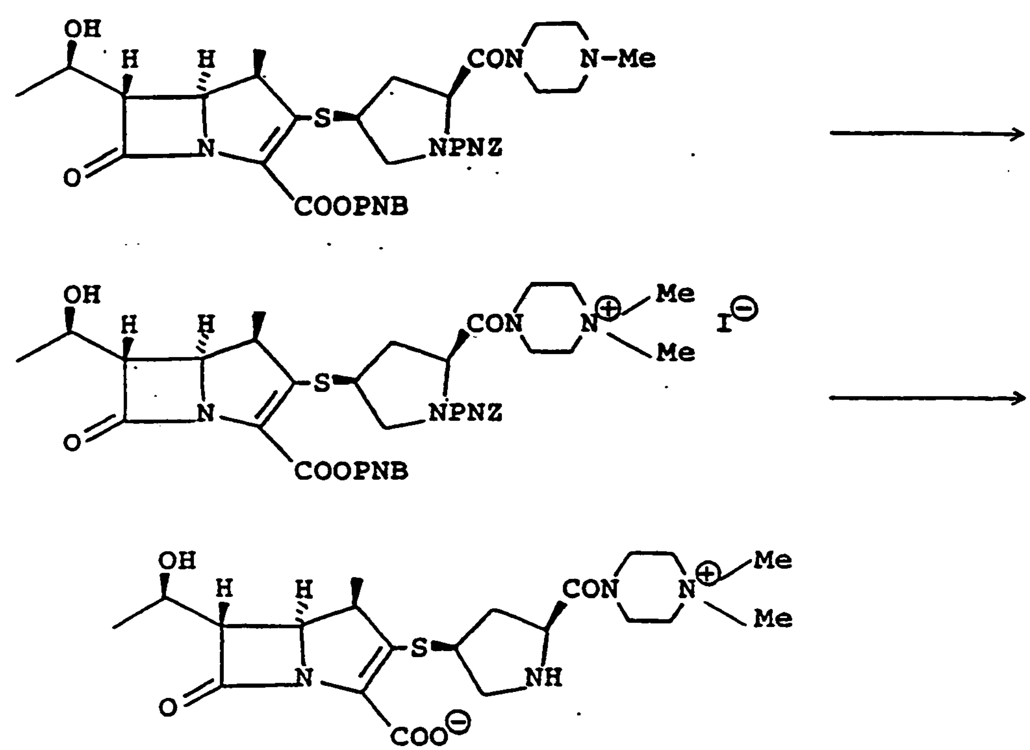


To a solution of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((2-(3-pyridyl)-ethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (270 mg) in acetone (25 ml), methyl iodide (3.42 g) was added, and the resultant mixture was stirred at room temperature for 3 hours, followed by removal of the solvent under reduced pressure. The residue was dissolved in tetrahydrofuran (15 ml) and 0.1M phosphate buffer (pH, 7.0; 15.0 ml), and 10 % palladium-carbon (500 mg) was added thereto. Catalytic reduction was performed at room temperature for 1 hour under atmospheric pressure of hydrogen. The reaction mixture was subjected to post-treatment in the same manner as in Example 1. The filtrate was purified by polymer chromatography (CHP-20P) using 2 % aqueous tetrahydrofuran as an eluent to give (4R,5S,6S,8R,2'S,4'S)-3-[2-((2-methylpyridinium-3-yl)ethyl)-methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

UV_{max} nm (H_2O): 268, 273, 298;

IR_{max} cm^{-1} (KBr):	3320, 1748, 1637, 1585, 1378;
NMR δ (D_2O):	1.20 (3H, d, J = 7.3 Hz), 1.27 (3H, d, J = 6.3 Hz), 2.81 (1H, m), 3.00 - 3.30 (5H, m), 3.09 (3H, s), 3.45 (3H, m), 3.79 (1H, m), 4.20 (4H, m), 4.38 (3H, s), 7.98 (1H, dd, J = 6.3 and 8.3 Hz), 8.44 (1H, d, J = 8.3 Hz), 8.69 (1H, d, J = 6.3 Hz), 8.79 (1H, s).

Example 3



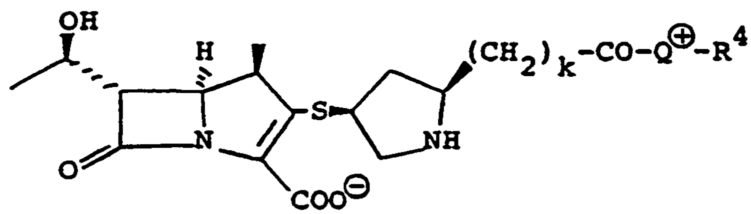
To a solution of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-methylpiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (200 mg) in acetone (2.0 ml), methyl iodide (1.14 g) was added, and the resultant mixture was stirred at room temperature for 20 hours, followed by removal of the solvent under reduced pressure. The residue was dissolved in tetrahydrofuran (10.0 ml) and 0.1M phosphate buffer (pH, 7.0; 10.0 ml), and 10 % palladium-carbon (241 mg) was added thereto. Catalytic reduction was performed at room temperature for 1.5 hours under atmospheric pressure of hydrogen. The reaction mixture was subjected to post-treatment in the same manner as in Example 1. The filtrate was purified by polymer chromatography (CHP-20P) using 1 % aqueous tetrahydrofuran as an eluent to give (4R,5S,6S,8R,2'S,4'S)-3-[2-(4,4-dimethylpiperazinium-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

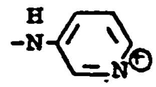
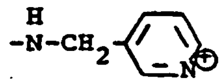
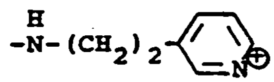
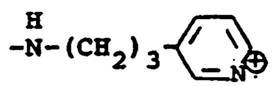
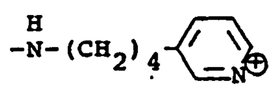
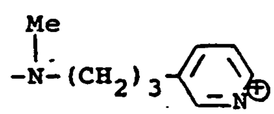
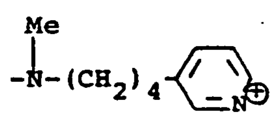
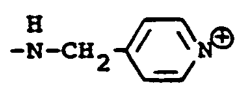
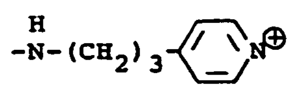
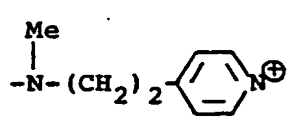
UV_{max} nm (H_2O):	299;
IR_{max} cm^{-1} (KBr):	3440, 1745, 1640, 1587, 1464, 1387, 1260;
NMR δ (D_2O):	1.21 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.6 Hz), 1.72 (1H, m), 2.78 (1H, m), 3.11 (1H, dd, J = 4.0 & 12.5 Hz), 3.27 (6N, s), 3.20 - 3.60 (9H, m), 3.80 - 4.20 (5H, m), 4.23 (3H, m).

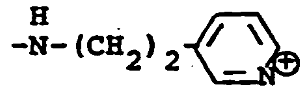
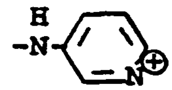
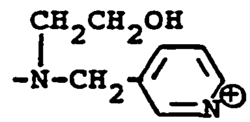
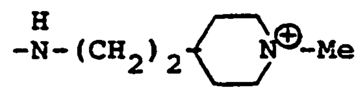
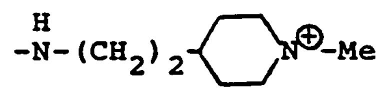
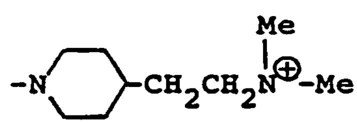
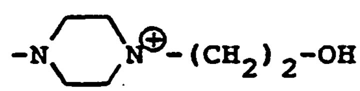
Examples 4 to 22

In the same manner as above, the compounds as shown in Table 2 were obtained. The physical properti s of the compounds as obtained follow the Table.

Table 2



Example No.	k	$Q^{\oplus}$	R^4
4	0		-Me
5	0		-Me
6	0		-Me
7	0		-Me
8	0		-Me
9	0		-Me
10	0		-Me
11	0		-Me
12	0		-Me
13	0		-Me
14	0		-Me

Example No.	k	$Q^{\oplus}$	R^4
15	1		-Me
16	2		-Me
17	0		-Me
18	1		-Me
19	0		-Me
20	1		-Me
21	0		-Me
22	0		-Me

Physical properties

Example 4

UV_{max} nm (H_2O):	252, 291;
IR_{max} cm^{-1} (KBr):	3380, 1737, 1580, 1502, 1364;
NMR δ (D_2O):	1.19 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.95 (1H, m), 2.73 (1H, m), 3.00 (1H, dd, J = 4.6 & 11.9 Hz), 3.40 (3H, m), 3.79 (1H, m), 4.09 (1H, dd, J = 5.6 & 9.6 Hz), 4,25 (2H, m), 4.40 (3H, s), 7.99 (1H, dd, J = 6.3 & 8.6 Hz), 8.47 (1H, d, J = 8.6 Hz), 8.53 (1H, d, J = 6.3 Hz), 9.27 (1H, s).

Example 5

UV_{max} nm (H_2O):	265, 273 (sh), 296;

IR_{max} cm^{-1} (KBr):	3360, 1730, 1670, 1590, 1385;
NMR δ (D_2O) :	1.19 (3H, d, J = 7.3 Hz), 1.25 (1H, m), 1.27 (3H, d, J = 6.3 Hz), 2.17 (1H, m), 3.02 (1H, m), 3.30 - 3.85 (4H, m), 4.08 (1H, m), 4.22 (2H, m), 4.37 (3H, s), 4.65 (3H, m), 8.02 (1H, t, J = 7.9 Hz), 8.46 (1H, d, J = 8.3 Hz), 8.71 (1H, d, J = 6.0 Hz), 8.77 (1H, s).

Example 6

UV_{max} nm (H_2O):	266, 272, 299;
IR_{max} cm^{-1} (KBr):	3300, 1750, 1652, 1588, 1380, 1366;
NMR δ (D_2O):	1.19 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.49 (1H, m), 2.69 (1H, m), 2.91 (1H, dd, J = 4.5 & 11.9 Hz), 3.10 (2H, t, J = 6.6 Hz), 3.30 - 3.50 (3H, m), 3.63 (2H, t, J = 5.9 Hz), 3.75 (1H, m), 3.93 (1H, dd, J = 6.3 & 9.6 Hz), 4.20 - 4.30 (2H, m), 4.37 (3H, s), 7.99 (1H, dd, J = 6.2 & 8.0 Hz), 8.44 (1H, d, J = 8.0 Hz), 8.67 (1H, d, J = 6.2 Hz), 8.77 (1H, s).

Example 7

UV_{max} nm (H_2O):	266, 273 (sh), 299;
IR_{max} cm^{-1} (KBr):	3410, 1749, 1640, 1588, 1380, 1278, 1255, 1178, 1140;
NMR δ (D_2O):	1.19 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.75 (1H, m), 1.96 (2H, m), 2.69 (1H, m), 2.89 (2H, m), 2.95 (1H, dd, J = 4.3 & 11.9 Hz), 3.20 - 3.50 (5H, m), 3.75 (1H, m), 3.87 (1H, dd, J = 6.3 & 9.5 Hz), 4.20 (2H, m), 4.35 (3H, s), 7.94 (1H, t, J = 7.0 Hz), 8.38 (1H, d, J = 7.9 Hz), 8.61 (1H, d, J = 6.0 Hz), 8.68 (1H, s).

Example 8

UV_{max} nm (H_2O):	266, 273, 299;
NMR δ (D_2O):	1.19 (3H, d, J = 7.0 Hz), 1.30 (3H, d, J = 6.6 Hz), 1.61 (2H, m), 1.73 (3H, m), 2.72 (1H, m), 2.89 (2H, m), 2.99 (1H, dd, J = 4.6 & 11.9 Hz), 3.29 (2H, m), 3.43 (3H, m), 3.79 (1H, m), 3.92 (1H, dd, J = 6.3 & 9.2 Hz), 4.23 (2H, m), 4.34 (3H, s), 7.93 (1H, dd, J = 6.3 & 8.3 Hz), 8.39 (1H, d, J = 8.3 Hz), 8.59 (1H, d, J = 6.3 Hz), 8.68 (1H, s).

Example 9

UV_{max} nm (H_2O):	268, 273, 297;
IR_{max} cm^{-1} (KBr):	3425, 1744, 1632, 1588, 1380, 1281;
NMR δ (D_2O):	1.21 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.82 (1H, m), 1.98 (2H, m), 2.86 (3H, m), 3.09 (3H, s), 3.20 - 3.70 (6H, m), 3.95 (1H, m), 4.24 (2H, m), 4.36 (3H, s), 4.48 (1H, dd, J = 6.9 & 9.6 Hz), 7.97 (1H, t, J = 7.0 Hz), 8.42 (1H, d, J = 7.6 Hz), 8.62 (1H, d, J = 6.3 Hz), 8.70 (1H, s).

Example 10

UV_{max} nm (H_2O):	268, 276, 296;
IR_{max} cm^{-1} (KBr):	3425, 1746, 1636, 1592, 1378, 1282, 1246;
NMR δ (D_2O):	1.18 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.66 (4H, m), 1.86 (1H, m), 2.93 (3H, m), 3.03 (3H, s), 3.20 - 3.80 (7H, m), 4.01 (1H, m), 4.23 (2H, m), 4.32 (3H, s), 7.92 (1H, t, J = 7.0 Hz), 8.39 (1H, d, J = 7.5 Hz), 8.56 (1H, d, J = 6.2 Hz), 8.65 (1H, s).

Example 11

UV_{max} nm (H_2O):	273, 300;
IR_{max} cm^{-1} (KBr):	3400, 1777, 1730, 1618;
NMR δ (D_2O):	1.20 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.6 Hz), 2.14 (1H, m), 2.68 (1H, m),

2.94 (1H, m), 3.25 - 3.50 (3H, m), 3.63 (1H, dd, J = 6.3 & 11.9 Hz), 3.73 (1H, m), 4.02 (1H, m), 4.23 (3H, s), 4.47 (1H, m), 8.10 (2H, d, J = 7.3 Hz), 8.57 (2H, d, J = 7.3 Hz).

Example 12

UV_{max} nm (H_2O):	258, 263 (sh), 297;
IR_{max} cm^{-1} (KBr):	3420, 1743, 1638, 1582, 1381;
NMR δ (D_2O):	1.19 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.6 Hz), 1.91 (1H, m), 2.76 (1H, m), 3.06 (1H, dd, J = 4.0 & 11.9 Hz), 3.43 (3H, m), 3.80 (1H, m), 4.10 (1H, dd, J = 5.9 & 9.7 Hz), 4.21 (2H, m), 4.34 (3H, s), 4.68 (1H, d, J = 18.2 Hz), 4.70 (1H, d, J = 18.2 Hz), 7.90 (2H, d, J = 6.3 Hz), 8.69 (2H, d, J = 6.3 Hz).

Example 13

UV_{max} nm (H_2O):	256, 263, 299;
IR_{max} cm^{-1} (KBr):	3410, 1743, 1639, 1584, 1376;
NMR δ (D_2O):	1.20 (3H, d, J = 7.3 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.79 (1H, m), 2.01 (2H, m), 2.72 (1H, m) , 2.99 (3H, m), 3.20 - 3.50 (5H, m), 3.79 (1H, m), 3.92 (1H, m), 4.30 (2H, m), 4.33 (3H, s), 7.89 (2H, d, J = 6.6 Hz), 8.62 (2H, d, J = 6.6 Hz).

Example 14

UV_{max} nm (H_2O):	257, 263 (sh), 300;
NMR δ (D_2O):	1.18 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.3 Hz), 1.80 (1H, m), 2.77 (1H, m), 3.05 (3H, s), 4.28 (3H, s), 7.93 (2H, d, J = 6.6 Hz), 8.64 (2H, d, J = 6.6 Hz).

Example 15

UV_{max} nm (H_2O):	269, 273, 296;
IR_{max} cm^{-1} (KBr):	3380, 1742, 1652, 1580, 1370, 1239, 1008;
NMR δ (D_2O):	1.18 (3H, d, J = 6.9 Hz), 1.26 (3H, d, J = 6.3 Hz), 1.92 (1H, m), 2.42 (1H, m), 2.56 (2H, m), 3.04 (3H, m), 3.25 - 3.70 (5H, m), 3.80 (1H, m), 3.96(1H, m), 4.26 (2H, m), 4.35 (3H, s), 7.95 (1H, t, J = 7.6 Hz), 8.40 (1H, d, J = 8.6 Hz), 8.65 (1H, d, J = 6.0 Hz), 8.72 (1H, s).

Example 16

UV_{max} nm (H_2O):	249, 294;
NMR δ (D_2O):	1.21 (3H, d, J = 6.9 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.70 (1H, m), 2.15 (2H, m), 2.73 (2H, m), 3.20 - 3.50 (3H, m), 3.50 - 3.85 (3H, m), 4.10 (1H, m), 4.18 (2H, m), 4.38 (3H, s), 7.92 (1H, m), 8.37 (1H, d, J = 7.9 Hz), 8.51 (1H, d, J = 5.9 Hz), 9.27 (1H, s).

Example 17

UV_{max} nm (H_2O):	267, 272, 300;
IR_{max} cm^{-1} (KBr):	3410, 1746, 1638, 1586, 1383;
NMR δ (D_2O):	1.22 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.70 (1H, m), 2.85 (1H, m), 3.12 (1H, dd, J = 3.6 & 12.2 Hz), 3.25 (1H, dd, J= 5.3 & 12.2 Hz), 3.43 (2H, m), 3.70 - 3.90 (5H, m), 4.24 (2H, m), 4.39 (1H, m), 4.40 (3H, s), 4.80 (1H, d, J = 16.5 Hz), 4.92 (1H, d, J = 16.5 Hz), 8.03 (1H, dd, J = 6.5 & 7.9 Hz), 8.43 (1H, d, J = 7.9 Hz), 8.71 (2H, m).

Example 18

UV_{max} nm (H_2O):	297;
IR_{max} cm^{-1} (KBr):	3400, 1748, 1639, 1586, 1453, 1372, 1257, 1088;

NMR δ (D_2O): 1.17 (3H, d, J = 7.3 Hz), 1.24 (3H, d, J = 6.3 Hz), 1.49 (1H, m), 2.61 (1H, m), 2.90 (2H, d, J = 6.9 Hz), 3.08 (1H, dd, J = 3.3 & 12.5 Hz), 3.21 (6H, s), 3.30 - 3.60 (7H, m), 3.73 (1H, t, J = 7.3 Hz), 3.90 (5H, m), 4.20 (2H, m).

Example 19

UV_{max} nm (H_2O): 300;
IR_{max} cm^{-1} (KBr): 3410, 1744, 1650, 1588, 1485, 1381, 1250, 1206, 1092;
NMR δ (D_2O): 1.22 (3H, d, J = 7.0 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.70 (6H, m), 2.00 (2H, m), 2.74 (1H, m), 3.04 (1H, dd, J = 5.0 & 12.2 Hz), 3.08 (3H, s), 3.15 (3H, s), 3.25 - 3.60 (9H, m), 3.81 (1H, m), 3.97 (1H, dd, J = 6.4 & 9.5 Hz), 4.24 (2H, m).

Example 20

UV_{max} nm (H_2O): 297;
IR_{max} cm^{-1} (KBr): 3400, 1742, 1635, 1582, 1479, 1363, 1241, 1201, 1082;
NMR δ (D_2O): 1.28 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.70 (6H, m), 1.97 (2H, m), 2.72 (1H, m), 2.79 (1H, m), 3.08 (3H, s), 3.15 (3H, s), 3.23 - 3.70 (10H, m), 4.02 (2H, m), 4.31 (2H, m).

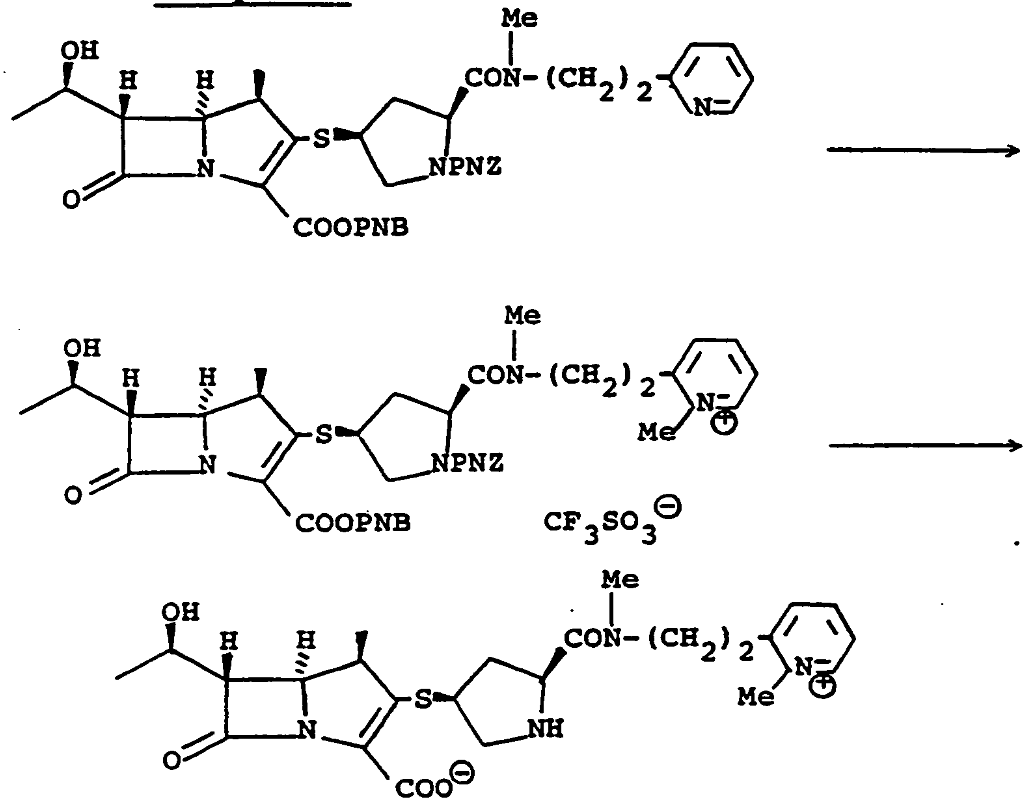
Example 21

UV_{max} nm (H_2O): 295;
IR_{max} cm^{-1} (KBr): 3440, 1758, 1644, 1597, 1492, 1379, 1258;
NMR δ (D_2O): 1.21 (3H, d, J = 7.0 Hz), 1.29 (3H, d, J = 6.6 Hz), 1.80 (7H, m), 2.86 (1H, m), 3.02 (1H, m), 3.11 (9H, s), 3.18 (2H, m), 3.39 (5H, m), 3.60 (1H, m), 3.80 (1H, m), 3.99 (1H, m), 4.24 (2H, m), 4.34 (1H, m), 4.64 (1H, m).

Example 22

UV_{max} nm (H_2O): 297;
IR_{max} cm^{-1} (KBr): 3400, 1743, 1637, 1588, 1380;
NMR δ (D_2O): 1.22 (3H, d, J = 6.9 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.68 (1H, m), 3.10 (1H, dd, J = 4.0 & 12.5 Hz), 2.76 (1H, m), 3.24 (1H, dd, J = 5.4 & 12.5 Hz), 3.31 (3H, s), 3.43 (2H, m), 3.68 (8H, m) 3.86 (1H, m), 3.97 (2H, m), 4.12 (2H, m), 4.25 (3H, m).

Example 23



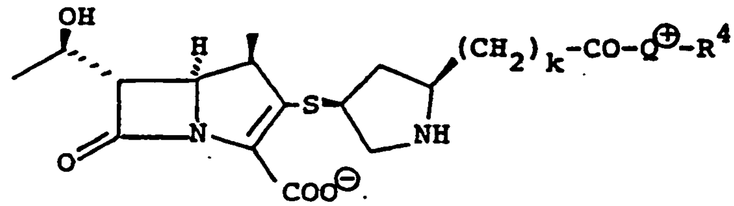
A solution of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-(p-nitrobenzyloxycarbonyl-2-((2-(2-pyridyl)ethyl)-methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (208 mg) in dry dichloromethane (3.0 ml) was stirred under ice-cooling, and methyl trifluoromethanesulfonate (64 mg) was dropwise added thereto, followed by stirring at the same temperature for 1 hour. The reaction mixture was combined with tetrahydrofuran (10.0 ml), 0.1M phosphate buffer (pH, 7.0; 10.0 ml) and 10 % palladium-carbon (350 mg), and catalytic reduction was performed at room temperature for 1 hour under atmospheric pressure of hydrogen. The reaction mixture was subjected to post-treatment in the same manner as in Example 1. The filtrate was purified by polymer chromatography (CHP-20P) using 2 % aqueous tetrahydrofuran as an eluent to give (4R,5S,6S,8R,2'S,4'S)-3-[2-((2-(1-methylpyridinium-2-yl)ethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

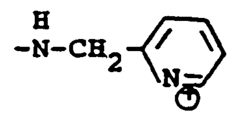
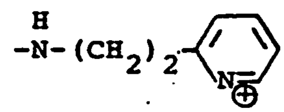
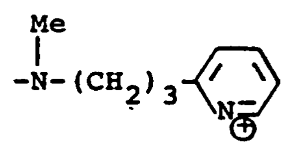
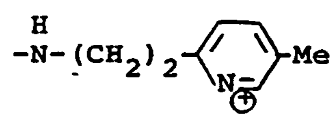
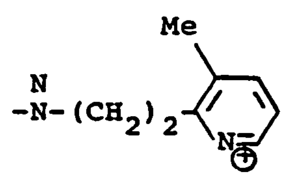
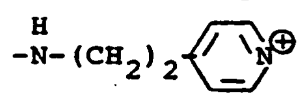
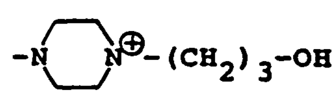
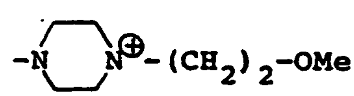
UV_{max} nm (H_2O):	269, 274, 298;
IR_{max} cm^{-1} (KBr):	3450, 1737, 1625, 1580, 1372, 1251, 1153;
NMR δ (D_2O):	1.20 (3H, d, J = 7.2 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.60 (1H, m), 3.00 (1H, m), 3.16 (3H, s), 3.26 (1H, dd, J = 3.3 & 12.2 Hz), 3.30 - 3.60 (5H, m), 3.65 (1H, m), 3.94 (1H, m), 4.13 (1H, m), 4.23 (2H, m), 4.40 (3H, s), 4.52 (1H, dd, J = 7.2 & 9.9 Hz), 7.90 (1H, d, J = 7.9 Hz), 7.92 (1H, t, J = 6.0 Hz), 8.45 (1H, t, J = 7.9 Hz), 8.76 (1H, d, J = 6.0 Hz).

Examples 24 to 31

In the same mann r as in Exampl 23, the compounds as shown in Table 3 were obtained. Th physical properties of the compounds as obtained follow the Table.

Table 3



Example No.	k	Q⊕	R^4
24	0		-Me
25	0		-Me
26	0		-Me
27	0		-Me
28	0		-Me
29	0		-Me
30	0		-Me
31	0		-Me

Physical properties

Example 24

UV$_{max}$ nm (H_2O): 267, 274 (sh), 298;
IR$_{max}$ cm^{-1} (KBr): 3430, 1743, 1679, 1577, 1380, 1260, 1158;
NMR δ (D_2O): 1.21 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.3 Hz), 2.20 (1H, m), 3.03 (1H, m), 3.03 - 3.60 (3H, m), 3.76 (1H, dd, J = 6.3 & 12.2 Hz), 4.07 (1H, m), 4.23 (2H, m), 4.34 (3H, s), 4.64 (1H, dd, J = 6.6 & 8.9 Hz), 4.89 (1H, d, J = 18.2 Hz), 4.90 (1H, d, J = 18.2 Hz), 7.95 (1H, t, J = 7.0 Hz) 7.96 (1H, d, J = 8.0 Hz), 8.52 (1H, t, J = 8.0 Hz), 8.79 (1H, d, J = 6.3 Hz).

Example 25

UV$_{max}$ nm (H_2O): 268, 273 (sh), 297;
IR$_{max}$ cm^{-1} (KBr): 3440, 1750, 1672, 1630, 1580, 1379, 1270;
NMR δ (D_2O): 1.19 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J =6.3 Hz), 1.88 (1H, m), 2.89 (1H, m), 3.30 - 3.50 (5H, m), 3.70 (2H, m), 3.85 (1H, dd, J = 6.9 & 14.2 Hz), 4.00 (1H, m), 4.24 (2H, m), 4.36 (3H, s), 4.41 (1H, dd, J = 6.6 & 9.6 Hz), 7.90 (2H, m), 8.46 (1H, t, J = 6.6 Hz), 8.76 (1H, d, J = 6.1 Hz).

Example 26

UV$_{max}$ nm (H_2O): 267, 273 (sh), 296;
IR$_{max}$ cm^{-1} (KBr): 3450, 1745, 1640, 1584, 1380, 1255, 1159;
NMR δ (D_2O): 1.21 (3H, d, J = 6.9 Hz), 1.30 (3H, d, J = 6.3 Hz), 2.03 (1H, m), 2.14 (2H, m), 3.20 - 3.30 (3H, m), 3.19 (3H, s), 3.30 - 3.70 (4H, m), 3.80 (2H, m), 4.10 (1H, m), 4.28 (2H, m), 4.30 (3H, s), 7.86 (1H, t, J = 6.6 Hz), 7.98 (1H, d, J = 8.3 Hz), 8.45 (1H, t, J = 7.6 Hz), 8.72 (1H, d, J = 5.6 Hz).

Example 27

UV$_{max}$ nm (H_2O): 296, 270 (sh), 265;
IR$_{max}$ cm^{-1} (KBr): 3430, 1740, 1669, 1578, 1441, 1378, 1267, 1246, 1157;
NMR δ (D_2O): 1.21 (3H, d, 3 = 7.2 Hz), 1.30 (3H, d, J = 6.6 Hz), 1.78 (1H, m), 2.75 (3H, s), 2.90 (1H, m), 3.09 (2H, m), 3.30 - 3.60 (5H, m), 3.68 (1H, dd, J = 6.0 & 12.2 Hz), 3.79 (1H, m), 4.01 (1H, m), 4.21 (3H, s), 4.23 (2H, m), 4.42 (1H, dd, J = 6.0 & 9.6 Hz), 7.87 (1H, d, J = 7.9 Hz), 8.30 (1H, dd, J = 1.3 & 7.9 Hz), 8.68 (1H, d, J = 1.3 Hz).

Example 28

UV$_{max}$ nm (H_2O): 278, 296;
IR$_{max}$ cm^{-1} (KBr): 3430, 1753, 1677, 1592, 1450, 1382, 1278, 1254, 1224, 1156;
NMR δ (D_2O): 1.22 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.6 Hz), 1.81 (1H, m), 2.83 (3H, s), 2.89 (1H, m), 3.17 (2H, m), 3.38 (2H, m), 3.50 (2H, m), 3.72 (2H, m), 4.00 (1H, m), 4.24 (2H, m), 4.28 (3H, s), 4.39 (1H, dd, J = 6.6 & 9.3 Hz), 7.80 (1H, t, J = 7.2 Hz), 8.29 (1H, d, J = 7.6 Hz), 8.63 (1H, d, J = 5.3 Hz).

Example 29

UV$_{max}$ nm (H_2O): 300, 264, 257, 228;
IR$_{max}$ cm^{-1} (KBr): 3400 (br), 1746, 1640, 1582, 1381, 1266;
NMR δ (D_2O): 1.21 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.56 (1H, m), 2.73 (1H, m), 2.97 (1H, dd, J = 4.6 & 12.2 Hz), 3.20 (2H, m), 3.40 (3H, m), 3.75 (1H, m), 4.00 (1H, dd, J = 6.0 & 9.6 Hz) 4.24 (3H, m), 4.34 (3H, s), 7.95 (2H, d, J = 6.6 Hz), 8.69 (2H, d, J = 6.6 Hz).

Example 30

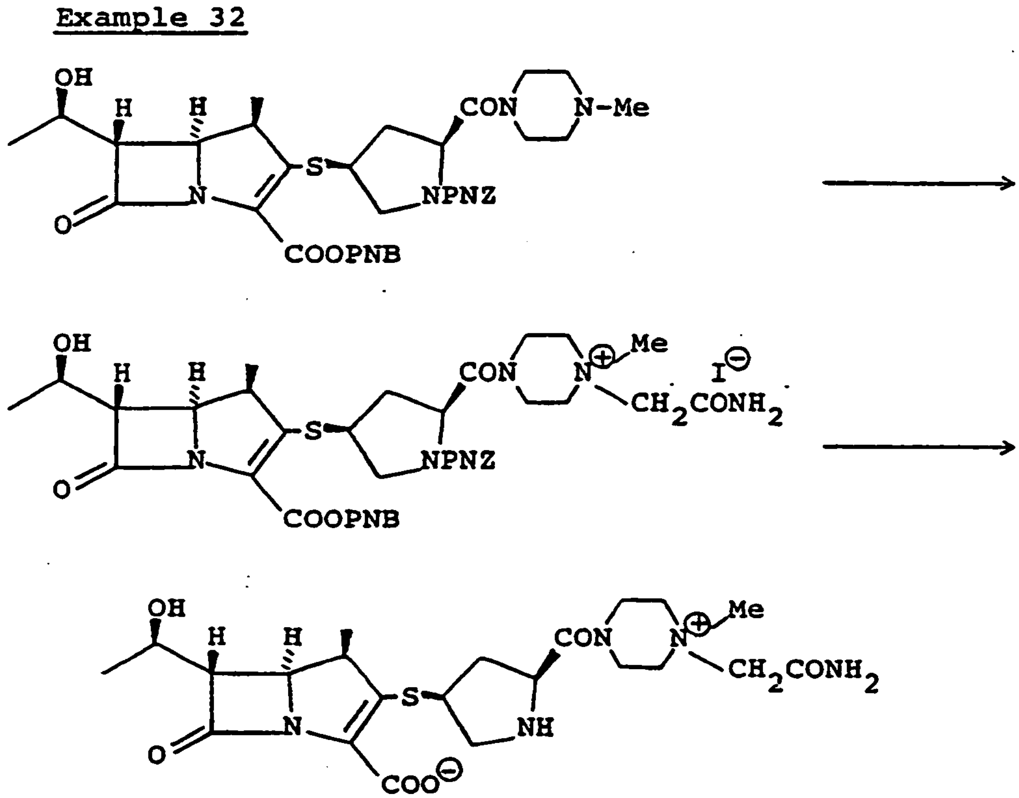
UV$_{max}$ nm (H_2O): 294;
IR$_{max}$ cm^{-1} (KBr): 3400, 1749, 1640, 1588, 1382, 1252;

NMR δ (D_2O):	1.22 (3H, d, J = 7.3 Hz), 1.31 (3H, d, J = 6.6 Hz), 1.76 (1H, m), 2.10 (2H, m), 2.81 (1H, m), 3.20 (2H, m), 3.24 (3H, s), 3.43 (1H, m), 3.61 (7H, m), 3.73 (2H, m), 3.92 (3H, m), 4.27 (5H, m).

Example 31

UV_{max} nm (H_2O):	292;
IR_{max} cm^{-1} (KBr):	3430, 1752, 1640, 1592, 1390, 1260;
NMR δ (D_2O):	1.24 (3H, d, J = 7.3 Hz), 1.32 (3H, d, J = 6.3 Hz), 1.69 (1H, m), 2.80 (1H, m), 3.12 (1H, dd, J = 3.3 & 12.9 Hz), 3.24 (1H, dd, J = 5.0 & 12.9 Hz), 3.31 (3H, s), 3.43 (3H, s), 3.44 (2H, m), 3.52 - 4.10 (13H, m), 4.29 (3H, m).

Example 32



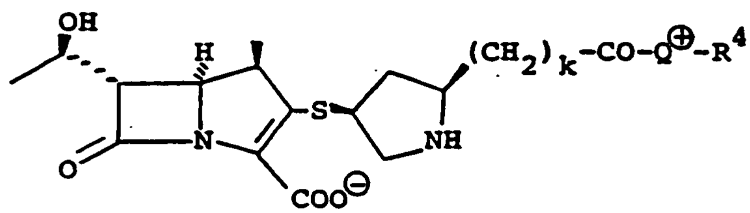
To a solution of (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-methylpiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (200 mg) in acetone (3.0 ml), iodoacetamide (200 mg) was added at room temperatuere, and the resultant mixture was stirred at the same temperature for 20 hours and concentrated under reduced pressure. The residue was combined with ethyl acetate (20 ml), stirred and allowed to stand. After removal of the supernatant by decantation, the insoluble material was dissolved in tetrahydrofuran (10 ml) and 0.1M phosphate buffer (pH, 7.0; 10 ml), followed by addition of 10 % palladium-carbon (430 mg). Catalytic reduction was performed at room temperature for 2 hours under ordinary or autogenic pressure. The reaction mixture was subjected to post-treatment in the same manner as in Example 1. The filtrate was purified by polymer chromatography (CHP-20P) using 1 % aqueous tetrahydrofuran as an eluent to give (4R,5S,6S,8R,2'S,4'S)-3-[2-(4-aminocarbonylmethyl -4-methylpiperazinium-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxy thyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

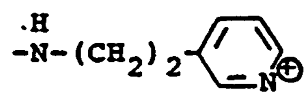
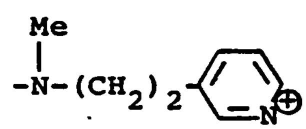
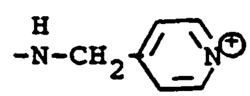
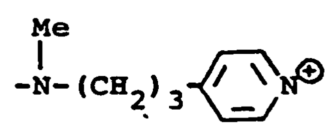
UV_{max} nm (H_2O):	297;
IR_{max} cm^{-1} (KBr):	3400, 1740, 1692, 1652, 1441, 1400, 1253, 1177, 1136;
NMR δ (D_2O):	1.23 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 2.05 (1H, m), 3.10 (1H, m), 3.45 (3H, s), 3.48 (3H, m), 3.70 - 4.40 (13H, m).

Examples 33 to 37

In th sam manner as in Exampl 32, the compounds as shown in Table 4 were obtained. Th physical properties of the compounds obtained follow the Table.

Table 4



Exmaple No.	k	$Q^{\oplus}$	R^4
33	0		$-CH_2CONH_2$
34	0		$-CH_2CONH_2$
35	0		$-CH_2CONH_2$
36	1		$-CH_2CONH_2$
37	0		$-CH_2CONH_2$

Physical properties

Example 33

UV_{max} nm (H_2O):	273, 294;
IR_{max} cm^{-1} (KBr):	3380, 1742, 1677, 1580, 1434, 1380, 1275, 1242;
NMR δ (D_2O):	1.20 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 1.77 (1H, m), 2.80 (1H, m), 3.14 (2H, m), 3.33 (2H, m), 3.45 (1H, dd, J = 2.6 & 6.3 Hz), 3.50 - 3.75 (2H, m), 3.78 (1H, dd, J = 6.3 & 13.5 Hz), 4.20 - 4.40 (3H, m), 5.50 (2H, s), 8.09 (1H, dd, J = 6.3 & 8.3 Hz), 8.58 (1H, d, J = 8.3 Hz), 8.70 (1H, d, J = 6.3 Hz), 8.78 (1H, s).

Example 34

UV_{max} nm (H_2O):	271, 294;
IR_{max} cm^{-1} (KBr):	3390, 1751, 1693, 1638, 1592, 1378;
NMR δ (D_2O):	1.20 (3H, d, J = 7.3 Hz), 1.28 (3H, J = 6.3 Hz), 1.54 (1H, m), 3.02 (1H, m), 3.03 (3H, s), 3.22 (2H, m), 3.36 (2H, m), 3.46 (1H, dd, J= 2.6 & 5.9 Hz), 3.61 (2H, m), 3.97 (1H, m), 4.12 (1H, m), 4.24 (2H, m), 4.74 (1H, m), 5.50 (2H, s), 8.08 (1H, dd, J = 6.3 & 8.2 Hz),8.60 (1H, d, J = 8.2 Hz), 8.71 (1H, d, J = 6.3 Hz), 8.79 (1H, s).

Example 35

UV_{max} nm (H_2O):	259, 265 (sh), 297;
IR_{max} cm^{-1} (KBr):	3400, 1748, 1682, 1639, 1545, 1388, 1279;
NMR δ (D_2O):	1.23 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 2.28 (1H, m), 3.05 (1H, m), 3.35 - 3.60 (3H, m), 3.84 (1H, dd, J = 7.3 & 12.2 Hz), 4.10 - 4.45 (3H, m), 5.51 (2H, s), 8.02 (2H, d, J = 7.0 Hz) 8.75 (2H, d, J = 7.0 Hz).

Example 36

UV_{max} nm (H_2O):	297;
IR_{max} cm^{-1} (KBr):	3380, 1747, 1687, 1636, 1586, 1444, 1378, 1244, 1089;
NMR δ (D_2O):	1.17 (3H, d, J = 7.3 Hz), 1.24 (3H, d, J = 6.3 Hz), 1.54 (1H, m), 2.63 (1H, m), 2.93 (2H, br.d, J = 6.6 Hz), 3.12 (1H, br.d, J = 12.5 Hz), 3.37 (3H, s), 4.23 (4H, m).

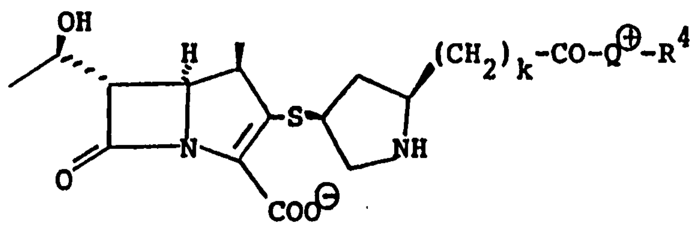
Example 37

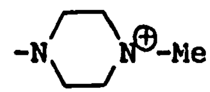
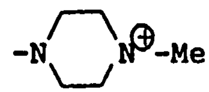
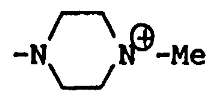
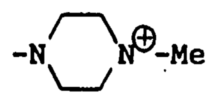
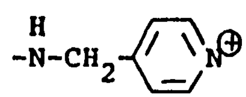
UV_{max} nm (H_2O):	299, 263 (sh), 256, 226 (sh);
IR_{max} cm^{-1} (KBr):	3400, 1746, 1691, 1637, 1584, 1387;
NMR δ (D_2O):	1.22 (3H, d, J = 7.3 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.62 (1H, m), 2.13 (2H, m), 2.86 (1H, m), 3.03 (2H, m), 3.08 (3H, s), 3.22 (2H, m), 3.45 (3H, m), 3.66 (1H, m), 3.87 (1H, m), 4.28 (3H, m), 5.52 (2H, s), 8.00 (2H, d, J = 6.9 Hz), 8.68 (2H, d, J = 6.9 Hz).

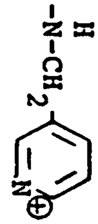
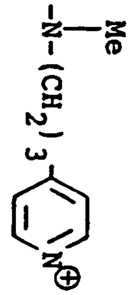
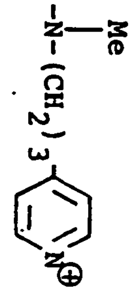
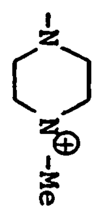
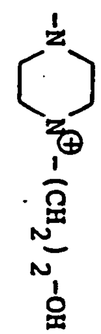
Examples 38 to 47

In the same manner as in Example 32 but using different alkylating agents (Y) in place of iodoacetamide, the compounds as shown in Table 5 were obtained. The physical properties of the compounds obtained follow the Table.

Table 5



Example No.	Y	k	$Q^{\oplus}$	R^4
38	$BrCH_2CONH-Me$	0		$-CH_2CONH-Me$
39	$BrCH_2CON(Me)Me$	0		$-CH_2CON(Me)Me$
40	$ICH_2CH_2CON(Me)Me$	0		$-CH_2CH_2CON(Me)Me$
41	$BrCH_2COOPNB$	0		$-CH_2COOH$
42	ICH_2COOH	0		$-CH_2COOH$

Example No.	Y	k	Q⊕	R^4
43	$PhCH_2Br$	0		$-CH_2Ph$
44	$BrCH_2COMe$	0		$-CH_2COMe$
45	ICH_2CH_2OH	0		$-CH_2CH_2OH$
46	$BrCH_2CO-Me$	0		$-CH_2CO-Me$
47	$BrCH_2COOPNB$	0		$-CH_2COOH$

Physical property

Example 38

UV$_{max}$ nm (H_2O): 299;
IR$_{max}$ cm^{-1} (KBr): 3410, 1736, 1638, 1362;
NMR δ (D_2O): 1.19 (3H, d, J = 7.3 Hz), 1.26 (3H, d, J = 6.3 Hz), 2.77 (3H, s), 3.15 (1H, dd, J = 3.3 & 12.2 Hz), 3.28 (1H, dd, J = 4.4 & 12.2 Hz), 3.38 (3H, s).

Example 39

UV_{max} nm (H_2O):	296;
IR_{max} cm^{-1} (KBr):	3400, 1746, 1644, 1589, 1378, 1253;
NMR δ (D_2O):	1.22 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.71 (1H, m), 2.78 (1H, m), 2.98 (3H, s), 3.05 (3H, s), 3.13 (1H, dd, J = 3.6 & 12.2 Hz), 3.25 (1H, dd, J = 4.0 & 12.2 Hz), 3.46 (3H, s), 4.53 (2H, br. s).

Example 40

UV_{max} nm (H_2O):	297;
IR_{max} cm^{-1} (KBr):	3430, 1745, 1633, 1583, 1480, 1369, 1242, 1087;
NMR δ (D_2O):	1.22 (3H, d, J = 7.3 Hz), 1.31 (3H, d, J = 6.6 Hz), 1.93 (1H, m), 2.96 (3H, s), 3.11 (3H, s), 3.26 (3H, s).

Example 41

UV_{max} nm (H_2O):	298;
IR_{max} cm^{-1} (KBr):	3420, 1745, 1627, 1592, 1448, 1382, 1254;
NMR δ (D_2O):	1.23 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.3 Hz), 1.82 (1H, m), 2.92 (1H, m), 3.42 (3H, s).

Example 42

UV_{max} nm (H_2O):	258, 266 (sh), 292;
NMR δ (D_2O):	1.22 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 2.21 (1H, m), 3.01 (1H, m), 3.38 (1H, m), 3.49 (3H, m) 3.79 (1H, dd, J = 6.6 & 12.2 Hz), 4.10 (1H, m), 4.26 (2H, m), 4.66 (2H, m), 5.21 (2H, s), 7.97 (2H, d, J = 6.9 Hz), 8.71 (2H, d, J = 6.9 Hz).

Example 43

UV_{max} nm (H_2O):	261, 266, 298;
IR_{max} cm^{-1} (KBr):	3400, 1753, 1672, 1596, 1367;
NMR δ (D_2O):	1.15 (3H, d, J = 7.3 Hz), 1.30 (3H, d, J = 6.6 Hz), 1.85 (1H, m), 2.72 (1H, m), 3.10 - 4.00 (5H, m), 4.25 (3H, m), 4.59 (1H, d, J = 15.9 Hz), 4.68 (1H, d, J = 15.9 Hz), 5.84 (2H, s), 7.60 (5H, m), 8.07 (1H, t, J = 7.9 Hz), 8.51 (1H, d, J = 8.5 Hz), 8.81 (1H, s), 8.87 (1H, d, J = 5.9 Hz).

Example 44

UV_{max} nm (H_2O):	299, 264 (sh), 257, 230;
IR_{max} cm^{-1} (KBr):	3410 (br), 1745, 1638, 1593, 1378;
NMR δ (D_2O) :	1.22 (3H, d, J = 7.6 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.66 (1H, m), 2.16 (2H, m), 2.44 (3H, s), 2.90 (1H, m), 3.07 (3H, s), 3.68 (1H, m), 3.87 (1H, m), 4.27 (4H, m), 8.00 (2H, d, J = 6.9 Hz), 8.53 (2H, d, J = 6.9 Hz).

Example 45

UV_{max} nm (D_2O):	296, 261, 255, 223;
IR_{max} cm^{-1} (KBr):	3425, 1751, 1639, 1592, 1304;
NMR δ (D_2O):	1.23 (3H, d, J = 7.3 Hz), 1.32 (3H, d, J = 6.3 Hz), 1.62 (1H, m), 2.12 (2H, m), 2.86 (1H, m), 2.97 (2H, m), 3.09 (3H, s), 3.20 (2H, m), 3.44 (4H, m), 3.62 (1H, m), 3.90 (1H, m), 4.08 (2H, m), 4.26 (4H, m), 7.97 (2H, d, J = 6.6 Hz), 8.72 (2H, d, J = 6.6 Hz).

Example 46

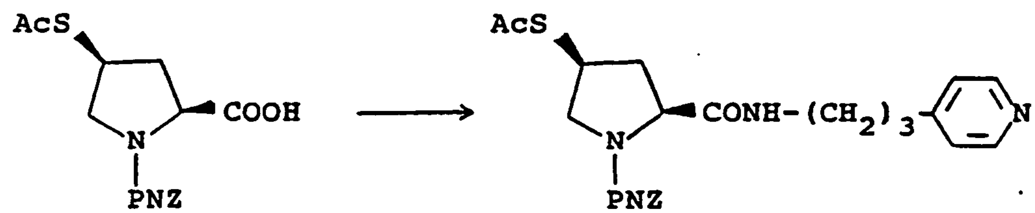
Uv_{max} nm (H_2O):	296;
IR_{max} cm^{-1} (KBr):	3400 (br), 1743, 1724, 1630, 1593, 1380, 1251;

NMR δ (D_2O): 1.20 (3H, d, J = 7.3 Hz), 1.28 (3H, d, J = 6.3 Hz), 1.70 (1H, m), 2.26 (3H, s), 2.77 (1H, m), 3.07 (1H, dd, J = 12.5 & 3.6 Hz), 3.19 (1H, dd, J = 12.5 & 6.6 Hz), 3.39 (3H, s), 3.40 (1H. m), 3.60 - 4.10 (11H, m), 4.23 (4H, m).

Example 47

UV_{max} nm (H_2O): 297;
IR_{max} cm^{-1} (KBr): 3400 (br), 1742, 1624, 1590, 1382;
NMR δ (D_2O): 1.24 (3H, d, J = 7.3 Hz), 1.31 (3H, d, J = 6.3 Hz), 1.85 (1H, m), 2.92 (1H, m), 3.28 (1H, m), 3.47 (5H, m), 3.80 - 4.37 (15H, m), 4.52 (1H, m).

Reference Example 1



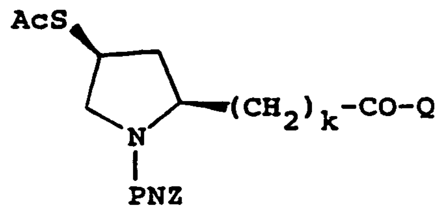
To a solution of cis-1-(p-nitrobenzyloxycarbonyl)-4-acetylthio-L-proline (552 mg; 1.5 mmol) and triethylamine (303 mg; 3.0 mmol) in dry tetrahydrofuran (6 ml), a solution of ethyl chloroformate (184 mg; 1.7 mmol) in dry tetrahydrofuran (1.5 ml) was dropwise added under ice-cooling, followed by stirring for 0.5 hour. To the reaction mixture, 4-(3-aminopropyl)pyridine (306 mg; 2.25 mmol) was added, and the resultant mixture was stirred for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with aqueous sodium hydrogen carbonate solution and aqueous sodium chloride solution in order and dried over anhydrous magensium sulfate-anhydrous sodium carbonate. After removal of the solvent, the residue was purified by silica gel chromatography to give (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-[3-(4-pyridylpropyl)-aminocarbonyl]-4-acetylthiopyrrolidine.

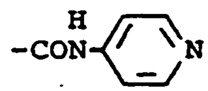
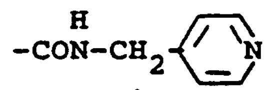
IR_{max} cm^{-1} (neat): 3300 (br), 1693, 1602, 1520, 1400, 1340, 1107;
NMR δ ($CDCl_3$): 2.32 (3H, s), 2.4 - 2.8 (4H, m), 3.2 - 3.5 (3H, m), 3.9 - 4.1 (1H, m), 4.1 - 4.2 (1H, m), 4.3 - 4.4 (1H, m), 5.25 (2H, s), 6.66 (1H, br.s), 7.10 (2H, d, J = 5.0 Hz), 7.49 (2H, d, J = 7.6 Hz), 8.20 (2H, d, J = 8.3 Hz), 8.49 (2H, m).

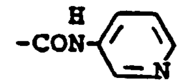
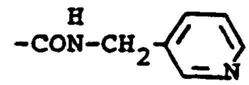
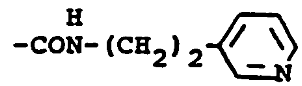
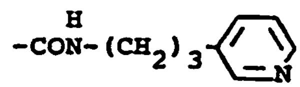
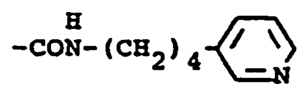
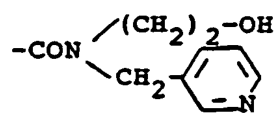
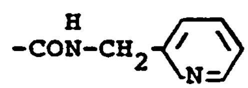
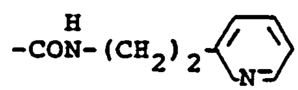
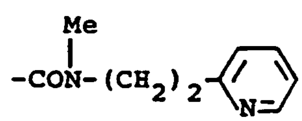
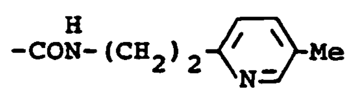
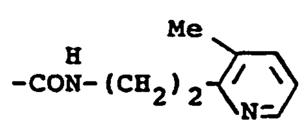
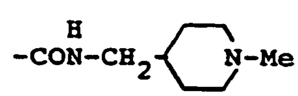
Reference Examples 2 to 16

In the same manner as in Reference Example 1, the thioacetates as shown in Table 6 were obtained from the corresponding amines. The physical properties of the compounds obtained follow the Table.

Table 6



Reference Example No.	$(CH_2)_k$-CO-Q
2	
3	

Refer nc Example No.	$(CH_2)_k-CO-Q$
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	

Reference Example 9

IR$_{max}$ cm^{-1} (CHCl$_3$): 3400 (br), 1690, 1685 (sh), 1655, 1521, 1422, 1345, 1200, 1120;
NMR δ (CDCl$_3$): 2.35 (3H, s), 3.2 - 3.6 (3H, m), 3.6 - 4.8 (8H, m), 4.8 - 5.2 (2H, m), 5.24 (2H, s), 7.2 - 7.5 (1H, m), 7.51 (2H, d, J = 8.9 Hz), 7.6 - 7.8 (1H, m), 8.23 (2H, d, J = 8.9 Hz), 8.4 - 8.7 (2H, m).

Reference Example 10

IR$_{max}$ cm^{-1} (KBr): 3310, 1767, 1700, 1653, 1518, 1435, 1344, 1260, 1240, 1172, 1098;
NMR δ (CDCl$_3$): 2.28 (1H, m), 2.30 (3H, s), 2.75 (1H, m), 3.44 (1H, m), 3.99 (1H, m), 4.21 (1H, m), 4.53 (3H, m), 5.12 (1H, m), 5.24 (2H, br. s), 7.2 - 7.7 (5H, m), 8.0 (1H, m), 8.23 (1H, m), 8.51 (1H, m).

Reference Example 11

NMR δ (CDCl$_3$): 2.20 (1H, m), 2.28 (3H, s), 2.98 (2H, m), 3.37 (1H, m), 3.64 (2H, m), 4.03 (1H, m), 5.23 (2H, m), 7.3 - 7.7 (4H, m), 8.03 (2H, m), 8.19 (1H, m), 8.42 (1H, m).

Reference Example 12

IR$_{max}$ cm^{-1} (neat): 3400, 1684, 1653, 1421, 1396, 1337, 1104;
NMR δ (CDCl$_3$): 1.82 (1H, m), 2.3 - 2.4 (3H, m), 2.5 - 3.25 (3H, m), 2.9 - 3.0 (3H, m), 3.45 (2H, m), 3.5 - 4.1 (5H, m), 4.13 (2H, m), 4.73 (1H, m), 5.23 (2H, m), 7.1 - 7.7 (4H, m), 8.20 (2H, m), 8.52 (1H, m).

Reference Example 13

IR$_{max}$ cm^{-1} (neat): 3300, 1675, 1595, 1510, 1415, 1392, 1333, 1284, 1247, 1198, 1160, 1103;
NMR δ (CDCl$_3$): 2.33 (3H, s), 2.35 (1H, m), 2.51 (3H, s), 2,78 (2H, m), 3.34 (1H, dd, J = 11.2 & 6.3 Hz), 3.50 (2H, m), 3.95 (1H, m), 4.10 (1H, dd, J = 8.6 & 6.9Hz), 4.31 (1H, dd, J = 8.6 & 5.6 Hz), 5.17 (1H, d, J = 13.5 Hz), 5.24 (1H, d, J = 13.5 Hz), 6.72 (1H, br. s), 7.09 (1H, d, J = 7.9 Hz), 7.3 - 7.7 (3H, m), 8,22 (2H, d, J = 8.2 Hz), 8.31 (1H, s).

Reference Example 14

IR$_{max}$ cm^{-1} (KBr): 3320, 1705, 1656, 1518, 1399, 1340, 1160, 1115;
NMR δ (CDCl$_3$): 1.65 (1H, m), 2.33 (3H, s),2.50 (1H, s), 2.57 (3H, s), 2.83 (2H, m), 3.34 (1H, dd, J = 10.8 & 5.9 Hz), 3.50 (2H, m), 3.97 (1H, m), 4.10 (1H, dd, J = 11.2 & 6.9 Hz), 4.34 (1H, dd, J = 7.9 & 6.3 Hz), 5.20 (2H, m), 7.06 (1H, dd, J = 3.9 & 7.6 Hz), 7.42 (1H, m), 7.50 (2H, m), 8.22 (2H, d; J = 8.6 Hz), 8.37 (1H, d, J = 3.9 Hz).

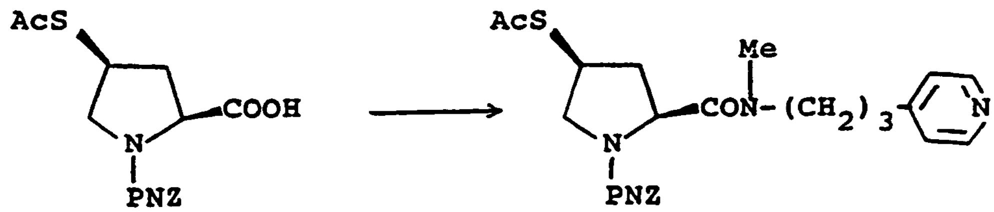
Reference Example 15

IR$_{max}$ cm^{-1} (KBr): 3320, 1700, 1665, 1605, 1550, 1518, 1428, 1402, 1342, 1178, 1118;
NMR δ (CDCl$_3$): 1.15 - 1.95 (7H, m), 2.24 (3H,s), 2.33 (3H, s), 2.4-2.7 (1H, m), 2.7 - 3.0 (2H, m), 3.0 - 3.3 (2H, m), 3.3 - 3.5 (1H, m), 3.9 - 4.5 (4H, m), 5.24 (2H, s), 6.65 (1H, br. s), 7.51 (2H, d, J = 8.4 Hz), 8.23 (2H, d, J = 8.4 Hz).

Reference Example 16

IR$_{max}$ cm^{-1} (KBr): 3290, 1707, 1687, 1645, 1522, 1421, 1340;
NMR δ (CDCl$_3$): 1.1 - 1.6 (5H, m), 1.6 - 2.0 (5H, m), 2.24 (3H, s), 2.33 (3H, s), 2.4 - 2.6 (1H, m), 2.82 (2H, d, J = 11.0 Hz), 3.2 - 3.6 (3H, m), 3.9 - 4.25 (2H, m), 4.3 - 4.5 (1H, m), 5.26 (2H, s), 6.51 (1H, br. s), 7.51 (2H, d, J = 8.3 Hz), 8.24 (2H, d, J = 8.3 Hz).

Reference Example 17



To a solution of cis-1-(p-nitrobenzyloxycarbonyl)-4-acetylthio-L-proline (736 mg; 2.0 mmol) in dry methylene chloride (6 ml), a catalytic amount of dimethylformamide was added, and a solution of oxalic chloride (305 mg; 2.4 mmol) in dry methylene chloride (2 ml) was added thereto. The resultant mixture was stirred at room temperature for 1 hour. Under ice-cooling, methyl [3-(4-pyridyl)propyl]amine (300 mg; 2.0 mmol) and a solution of triethylamine (485 mg; 4.8 mmol) in dry methylene chloride (2. ml) were added thereto, followed by stirring for 15 minutes. The reaction mixture was combined with aqueous sodium hydrogen carbonate solution, and the organic phase was separated from the aqueous phase, washed with aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (2S,4s)-1-(p-nitrobenzyloxycarbonyl)-2-[3-(4-pyridyl)propyl]methylaminocarbonyl-4-acetylthiopyrrolidine.

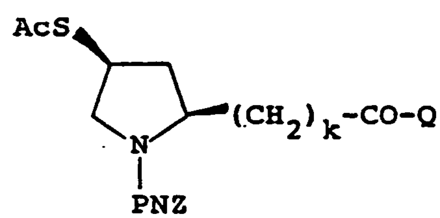
IR_{max} cm^{-1} (neat): 1715 (sh), 1700, 1654, 1600, 1518, 1340, 1160, 1107;

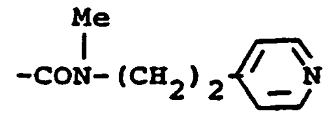
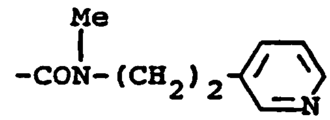
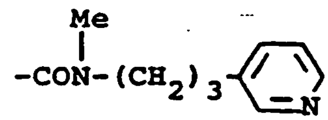
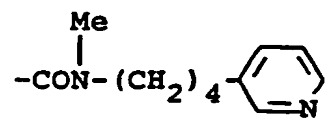
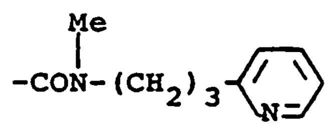
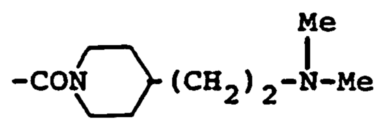
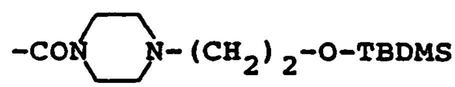
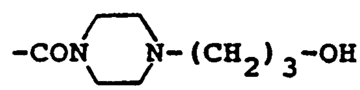
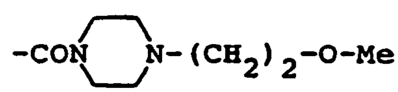
NMR δ ($CDCl_3$): 1.7 - 2.2 (3H, m), 2.33 (3H, s), 2.4 - 2.9 (3H, m) , 2.9 - 3.1 (3H, m), 3.3 - 3.7 (3H, m), 3.9 - 4.2 (2H, m), 4.5 - 4.8 (1H, m), 5.21 (2H, s), 6.9 - 7.2 (2H, m), 7.3 - 7.6 (2H, m), 8.1 - 8.3 (2H, m), 8.4 - 8.6 (2H, m).

Reference Examples 18 to 26

In the same manner as in Reference Example 17, the thioacetates as shown in Table 7 were obtained from the corresponding amines. The physical properties of the compounds obtained follow the Table.

Table 7



Refer nce Example No.	$(CH_2)_k$-CO-Q
18	
19	
20	
21	
22	
23	
24	
25	
26	

Physical properties

Reference Example 18

IR$_{max}$ cm^{-1} (neat): 1715 (sh), 1700, 1687 (sh), 1602, 1520, 1340, 1162, 1107;
NMR δ ($CDCl_3$): 1.7 - 2.0 (1H, m), 2.34 (3H, s), 2.5 - 3.1 (6H, m), 3.3 - 3.85 (3H, m), 3.85 - 4.2 (2H, m), 4.5 - 4.8 (1H, m), 5.22 (2H, s), 7.0 - 7.25 (2H, m), 7.4 - 7.6 (2H, m), 8.1 - 8.3 (2H, m), 8.45 - 8.65 (2H, m).

Reference Example 19

IR$_{max}$ cm^{-1} (n at): 1730 (sh), 1692 (sh), 1660, 1507, 1390, 1335, 1150, 1110;
NMR δ ($CDCl_3$): 1.6 - 1.9 (1H, m), 2.34 (3H, s), 2.5 - 3.1 (6H, m), 3.3 - 4.3 (5H, m), 4.5 - 4.8 (1H, m), 5.22 (2H, s), 7.2 - 7.4 (1H, m), 7.4 - 7.7 (3H, m), 8.22 (2H, d, J = 8.9 Hz), 8.47 (2H, br. s).

Reference Example 20

IR$_{max}$ cm^{-1} (neat): 2930, 1715 (sh), 1704, 1696 (sh), 1650, 1518, 1420, 1400, 1340, 1105;
NMR δ ($CDCl_3$): 1.7 - 2.2 (3H, m), 2.33 (3H, s), 2.4 - 2.85 (3H, m), 2.85 - 3.15 (3H, m), 3.3 - 3.6 (2H, m), 3.85 - 4.2 (2H, m), 4.45 - 4.8 (1H, m), 5.22 (2H, s), 7.1 - 7.3 (1H, m), 7.3 - 7.6 (3H, m), 8.05 - 8.3 (2H, m), 8.3 - 8.6 (2H, m).

Reference Example 21

IR$_{max}$ cm^{-1} (neat): 2925, 1714 (sh), 1682, 1654, 1518, 1420, 1400, 1340, 1160, 1115;
NMR δ ($CDCl_3$): 1.8 - 2.15 (2H, m), 2.33 (3H, s), 2.4 - 2.8 (3H, m), 2.8 - 3.1 (3H, m), 3.2 - 3.6 (3H, m), 3.9 - 4.2 (3H, m), 4.69 (1H, m), 5.20 (2H, m), 7.1 - 7.6 (4H, m), 8.1 - 8.3 (2H, m), 8.3 - 8.6 (2H, m).

Reference Example 22

IR$_{max}$ cm^{-1} (neat): 1720 (sh), 1705, 1650, 1515, 1430, 1400, 1340, 1110;
NMR δ ($CDCl_3$): 1.7 - 2.3 (2H, m), 2.33 (3H, s), 2.5 - 3.2 (7H, m), 3.2 - 3.7 (3H, m), 3.8 - 4.3 (2H, m), 5.6 - 5.8 (1H, m), 5.21 (2H, s), 7.0 - 7.3 (2H, m), 7.4 - 7.7 (3H, m), 8.0 - 8.3 (2H, m), 8.5 - 8.7 (1H, m).

Reference Example 23

IR$_{max}$ cm^{-1} (neat): 2920, 1700 (sh), 1688, 1642, 1507, 1400, 1336, 1100;
NMR δ ($CDCl_3$): 0.8 - 2.0 (10H, m), 2.21 (6H, s), 2.33 (3H, s), 2.5 - 3.2 (3H, m), 3.3 - 5.0 (5H, m), 5.22 (2H, s), 7.51 (2H, d, J = 8.5 Hz), 8.22 (2H, d, J = 8.5 Hz).

Reference Example 24

IR$_{max}$ cm^{-1} (neat): 1700, 1660, 1523, 1438, 1402, 1342, 1253, 1103;
NMR δ ($CDCl_3$): 0.05 (6H, s), 0.89 (9H, s), 1.88 (1H, m), 2.33 (3H, s), 2.50 (6H, m), 3.40 (2H, m), 3.55 (2H, m), 3.72 (1H, m), 3.75 (2H, m), 4.00 (1H, m), 4.13 (2H, m), 4.72 (1H, m), 5.05 - 5.40 (2H, m), 7.50 (2H, m), 8.23 (2H, m).

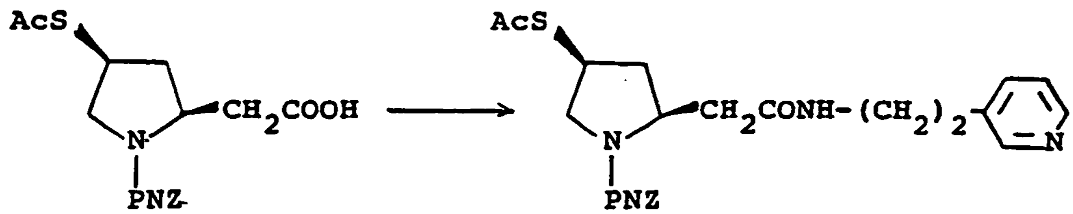
Reference Example 25

IR$_{max}$ cm^{-1} (neat): 3450 (br), 1700, 1653, 1521, 1435, 1342, 1120;
NMR δ ($CDCl_3$): 1.80 - 2.00 (1H, m), 2.2 - 2.9 (8H, m), 2.34 (3H, s), 3.3 - 3.9 (8H, m), 3.9 - 4.2 (2H, m), 4.6 - 4.8 (1H, m), 5.0 - 5.4 (2H, m), 7.51 (2H, d, J = 8.9 Hz), 8.22 (2H, d, J = 8.9 Hz).

Reference Example 26

NMR δ ($CDCl_3$): 1.90 (1H, m), 2.34 (3H, s), 2.30 - 2.85 (7H, m), 3.34 (3H x 0.3, s), 3.35 (3H x 0.7, s), 3.40 - 3.78 (7H, m), 4.01 (1H, m), 4.14 (1H, m), 4.75 (1H, m), 5.07 (0.3H, d, J = 13.9 Hz), 5.23 (2H x 0.7, s), 5.31 (0.3H, d, J = 13.9 Hz), 7.50 (2H,m) 8.23 (2H, m).

Reference Example 27



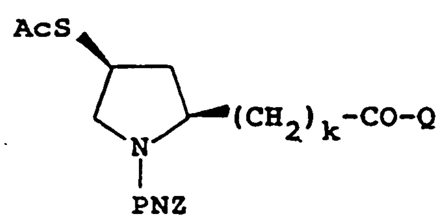
In the same manner as in Reference Example 1, there was obtained (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-[2-(3-pyridylethyl)aminocarbonyl]methyl-4-acetylthiopyrrolidine from (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-carboxymethyl-4-acetylthiopyrrolidine (382 mg; 1.0 mmol).

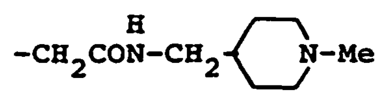
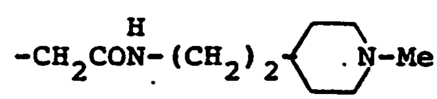
IR_{max} cm^{-1} (neat):	3295 (br), 1690 (sh), 1680, 1650 (sh), 1513, 1418, 1395, 1338, 1100;
NMR δ ($CDCl_3$):	2.2 - 2.7 (2H, m), 2.34 (3H, s), 2.7 - 3.0 (3H, m), 3.25 (1H, dd, J = 7.3 & 11.2 Hz), 3.4 - 3.7 (2H, m), 3.8 - 4.3 (3H, m), 5.19 (2H, s), 5.98 (1H, br.s), 7.15 - 7.35 (1H, m), 7.35 - 7.65 (3H, m), 8.22 (2H, d, J = 8.6 Hz), 8.4 - 8.6 (2H, m).

Reference Examples 28 and 29

In the same manner as in Reference Example 27, the thioacetates as shown in Table 8 were obtained from the corresponding amines. The physical properties of the compounds obtained follow the Table.

Table 8



Reference Example No.	$(CH_2)_k$-CO-Q
28	
29	

Physical properties

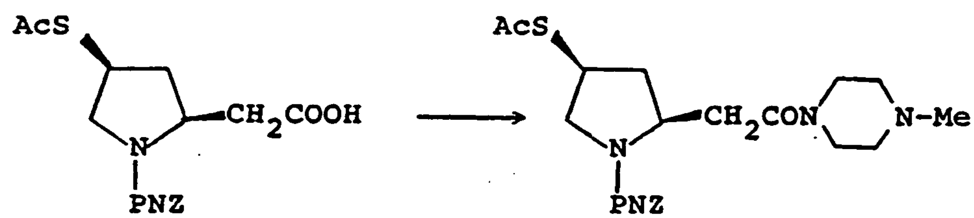
Reference Example 28

IR_{max} cm^{-1} (KBr):	3310, 1700, 1645, 1527, 1445, 1430, 1405, 1347, 1320, 1200, 1147, 1110;
NMR δ ($CDCl_3$):	1.15 - 1.55 (4H, m), 1.55 - 2.0 (5H, m), 2.25 (3H, s), 2.34 (3H, s), 2.4 - 2.7 (1H, m), 2.7 - 3.0 (3H, m), 3.0 - 3.6 (3H, m), 3.8 - 4.5 (3H, m), 5.21 (2H, s), 5.86 (1H, br. s), 7.52 (2H, d, J = 8.8 Hz), 8.23 (2H, d, J = 8.8 Hz).

Reference Example 29

IR_{max} cm^{-1} (KBr):	3290, 1690 (sh), 1687, 1630, 1520, 1424, 1342;
NMR δ ($CDCl_3$):	1.1 - 1.5 (5H, m), 1.5 - 1.8 (3H, m), 1.87 (2H, t, J = 10.7 Hz), 2.25 (3H, s), 2.34 (3H, s), 2.4 - 2.7 (2H, m), 2.7 - 3.0 (3H, m), 3.1 - 3.4 (3H, m), 3.8 - 4.3 (3H, m), 5.21 (2H, s), 5.71 (1H, br. s), 7.51 (2H, d, J = 8.6 Hz), 8.23 (2H, d, J = 8.6 Hz).

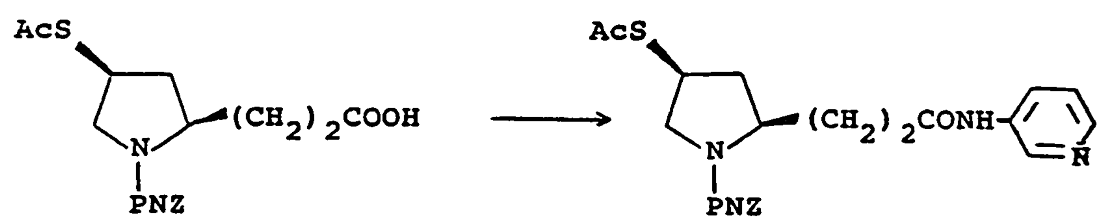
Reference Example 30



In the same manner as in Reference Example 2, there was obtained (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-[(4-methyl)piperazin-1-yl]carbonylmethyl-4-acetylthiopyrrolidine from (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-carboxymethyl-4-acetylthiopyrrolidine (382 mg; 1.0 mmol).

IR_{max} cm^{-1} (neat)	: 1687, 1634, 1515, 1420, 1398, 1340, 1285, 1100;
NMR δ ($CDCl_3$):	1.8 - 2.0 (1H, m), 2.2 - 2.6 (6H, m), 2.29 (3H, s), 2.34 (3H, s), 2.6 - 2.9 (1H, m), 3.2 - 3.8 (5H, m), 3.8 - 4.0 (1H, m), 4.0 - 4.5 (2H, m), 5.21 (2H, s), 7.51 (2H, d, J = 8.6 Hz), 8.23 (2H, d, J = 8.6 Hz).

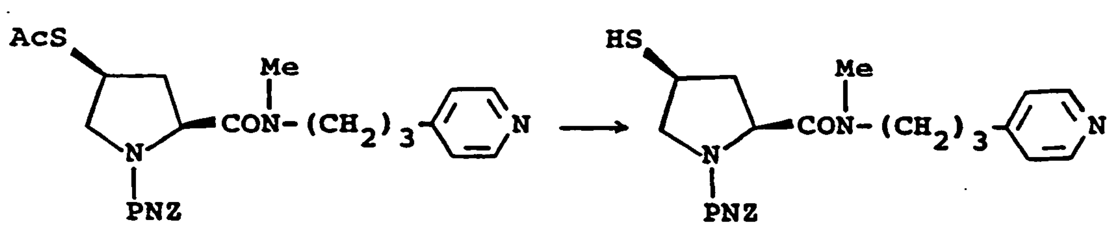
Reference Example 31



In the same manner as in Reference Example 2, there was obtained (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-(3-pyridylamino)carbonylethyl-4-acetylthiopyrrolidine from (2R,4S)-1-(p-nitrobenzyloxycarbonyl)-2-(2-carboxy)ethyl-4-acetylthiopyrrolidine (198 mg; 0.50 mmol).

IR_{max} cm^{-1} (neat):	3280 (br), 1700 (sh), 1680, 1516, 1400, 1338;
NMR δ ($CDCl_3$):	1.6 - 2.8 (6H, m), 2.35 (3H, s), 3.28 (1H, dd, J = 6.8 & 11.7 Hz), 3.92 (1H, m), 4.0 - 4.3 (2H, m), 5:26 (2H, s), 7.2 - 7.4 (2H, m), 7.53 (2H, d, J = 8.7 Hz), 8.25 (2H, d, J = 8.7 Hz), 8.3 - 8.45 (1H, m), 8.67 (1H, d, J = 2.3 Hz), 9.23 (1H, br. s).

Reference Example 32

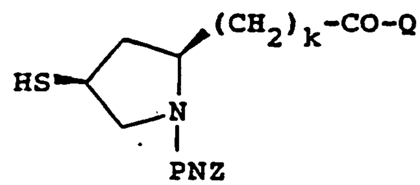


To a solution of (2S,4S)-1-(p-nitrobenzyloxycarbonyl)-2-(3-(4-pyridyl)propyl)methylaminocarbonyl)-4-acetylthiopyrrolidin (332 mg) in methanol (30 ml), 1N aqueous sodium hydroxide solution (0.70 ml) was

added at room temperatur , and the resultant mixtur was stirred for 10 minutes. 1N Hydrochloric acid (0.70 ml) was added to the reaction mixture, and m thanol was removed by distillation under reduced pressure. The residue was combined with dichloromethane, washed with water and dried over anhydrous magnesium sulfate, followed by removal of th solvent to give (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-(3-(4-pyridyl)-propyl)methylaminocarbonyl-4-mercaptopyrrolidine, which was subjected to the subsequent reaction without purification.

In the same manner as in Reference Example 32, the mercaptan compounds as shown in Table 9 were obtained from the corresponding thioacetates.

Table 9



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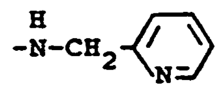
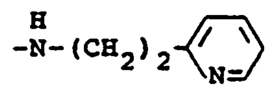
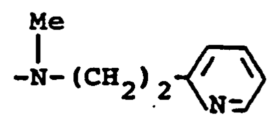
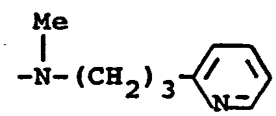
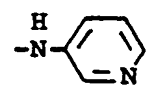
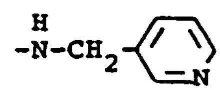
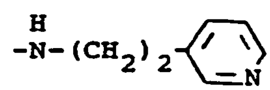
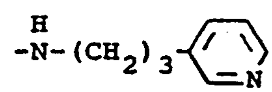
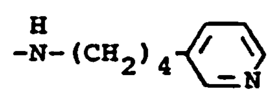
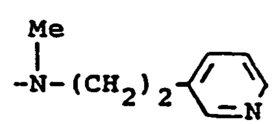
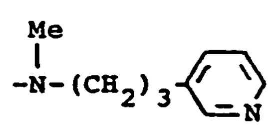
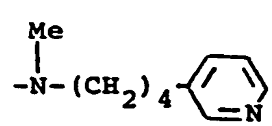
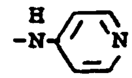
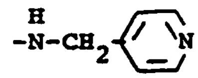
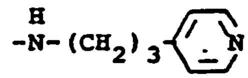
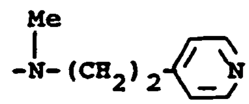
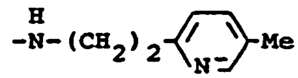
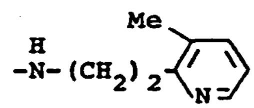
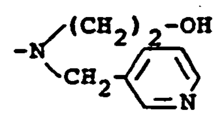
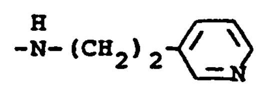
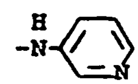
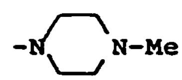
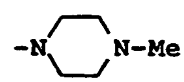
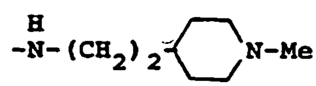
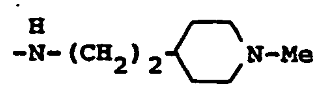
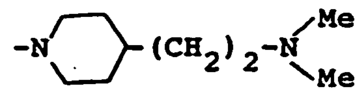
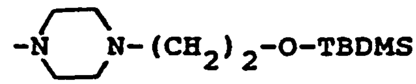
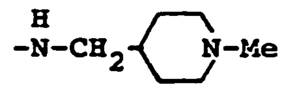
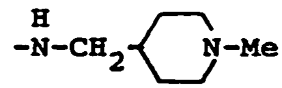
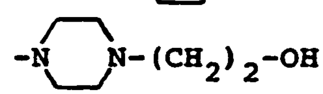
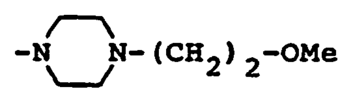
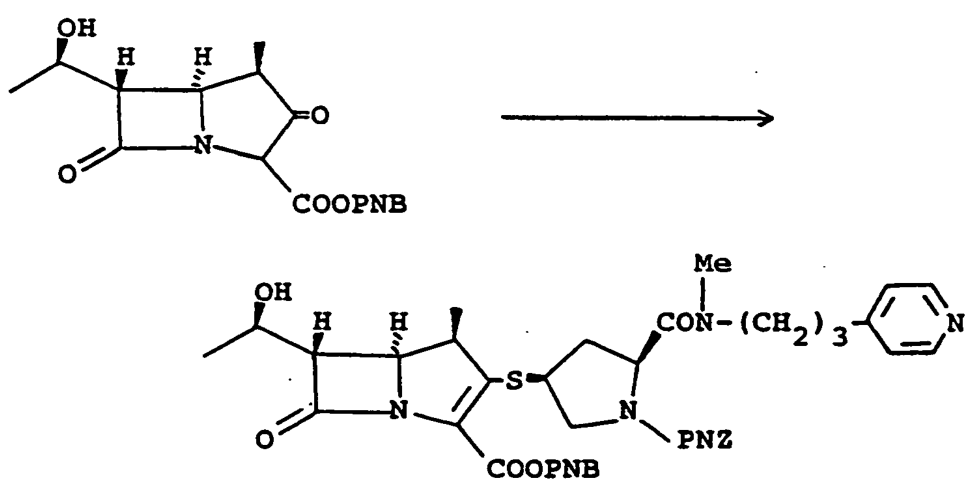
1	0	
2	0	
3	0	
4	0	
5	0	
6	0	
7	0	
8	0	
9	0	
10	0	
11	0	
12	0	

No.	k	Q
13	0	
14	0	
15	0	
16	0	
17	0	
18	0	
19	0	
20	1	
21	2	
22	0	
23	1	
24	0	
25	1	

No.	k	Q
26	0	
27	0	
28	0	
29	1	
30	0	
31	0	

Reference Example 33



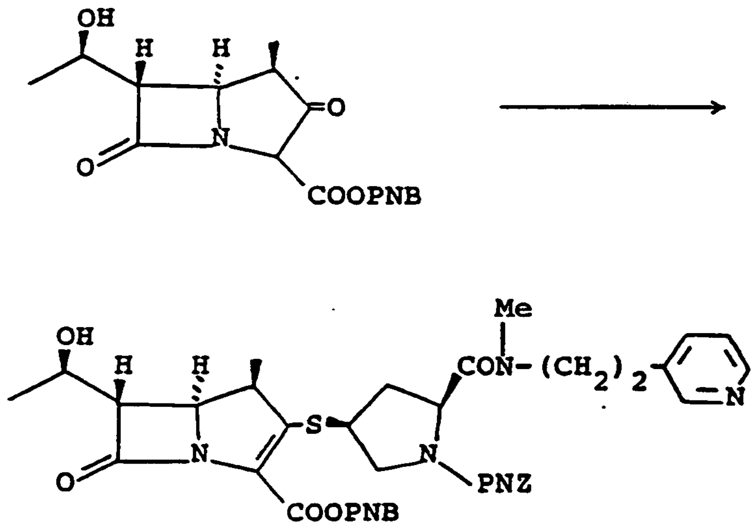
To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (218 mg) in dry acetonitrile (2.0 ml), diisopropylethylamine (94 mg) and diphenyl chlorophosphate (178 mg) were added under ice-cooling, and the resultant mixture was stirred at the same temperature for 2 hours. A solution of (2S,4S)-p-nitrobenzyloxycarbonyl-2-(3-(4-pyridyl)propyl)-methylaminocarbonyl-4-mercaptopyrrolidine (311 mg) and diisopropylethylamine (94 mg) in dry acetonitrile (3.0 ml) was add d to the reaction mixture, follow d by stirring for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with aqueous potassium phosphate solution and a saturated aqueous sodium chloride solution in order and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((3-(4-pyridyl)propyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-

hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

IR_{max} cm^{-1} (neat): 3380, 1763, 1700, 1644, 1601, 1517, 1403, 1339;

NMR δ ($CDCl_3$): 1.28 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.3 Hz), 3.08, 2.96 (3H as a whole, each s), 5.21 (2H, br.s), 5.24 (1H, d, J = 13.8 Hz), 5.51 (1H, d, J = 13.8 Hz), 6.97 - 7.20 (2H, m), 7.35 - 7.63 (2H, m), 7.65 (2H, d, J = 8.9 Hz), 8.10 - 8.30 (4H, m), 8.52 (2H, m).

Reference Example 34

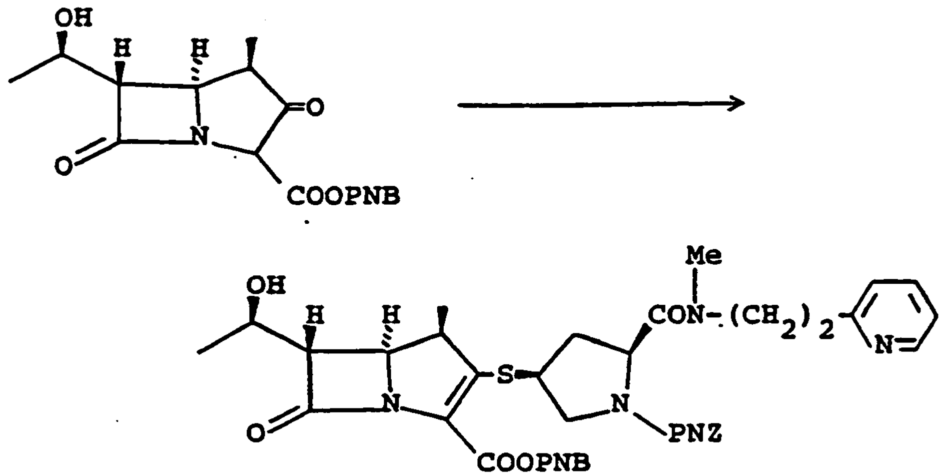


To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (54 mg) in dry acetonitrile (1.0 ml), diisopropylethylamine (22 mg) and diphenyl chlorophosphate (45 mg) were added under ice-cooling, and the resultant mixture was stirred at the same temperature for 1 hour. A solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-(2-(3-pyridyl)ethyl)-methylaminocarbonyl-4-mercaptopyrrolidine (95 mg) and diisopropylethylamine (22 mg) in dry acetonitrile (1.0 ml) was added to the reaction mixture, followed by stirring for 1.5 hours. The reaction mixture was diluted with dichloromethane, washed with water and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((2-(3-pyridyl)ethyl)-methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

IR_{max} cm^{-1} (neat): 3400, 1755, 1690, 1512, 1332;

NMR δ ($CDCl_3$): 1.27 (3H, d, J = 7.0 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.88, 2.96, 3.00 (3H as a whole, each s), 3.27 (1H, m), 5.30 (3H, m), 5.50 (1H, d, J = 13.5 Hz), 7.26 (1H, m), 7.4 - 7.6 (3H, m), 7.65 (2H, d, J = 8.6 Hz), 8.22 (4H, d, J = 8.6 Hz), 8.4 - 8.6 (2H, m).

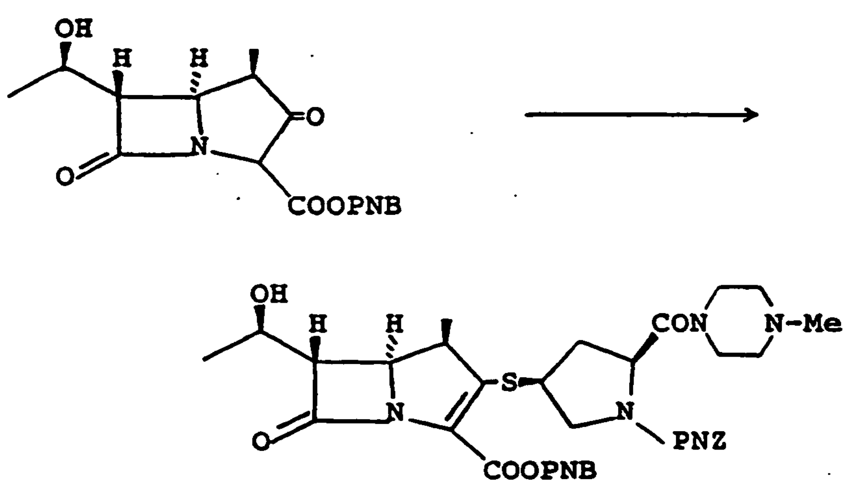
Reference Exampl 35



To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (181 mg) in dry acetonitrile (2.0 ml), diisopropylethylamine (81 mg) and diphenyl chlorophosphate (175 mg) were added under ice-cooling, and the resultant mixture was stirred at the sam temperature for 1 hour. A solution of (2S,4S)-p-nitrobenzyloxycarbonyl-2-(2-(2-pyridyl)ethyl)-methylaminocarbonyl-4-mercaptopyrrolidine (303 mg) in dry acetonitrile (3.0 ml) and then diisopropylethylamine (81 mg) were added to the reaction mixture, followed by stirring for 2 hours. Th reaction mixture was diluted with ethyl acetate, washed with aqueous potassium phosphate solution and a saturated aqueous sodium chloride solution in order and dried over magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((2-(2-pyridyl)ethyl)methylaminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

NMR δ ($CDCl_3$): 1.28 (3H, d, J = 7.3 Hz), 1.34 (3H, d, J = 6.3 Hz), 1.87 (1H, m), 2.73 (1H, m), 2.92, 2.93, 2.95, 3.01 (3H as a whole, each s), 4.80 (1H, m), 5.26 (3H, m), 5.49 (1H, d, J = 13.9 Hz), 7.00 - 7.75 (7H, m), 8.22 (4H, m), 8.50 (1H, m).

Reference Example 36



To a solution of (4R,5R,6S,8R)-1-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (2.55 g) in dry acetonitrile (10.0 ml), diisopropylethylamine (1.09 g) and diphenyl chlorophosphate (2.06 g) were added under ice-cooling, and the resultant mixture was stirred at the same

temperature for 2 hours. A solution of (2S,4S)-p-nitrobenzyloxycarbonyl-2-(4-methylpiperazin-1-ylcarbonyl)-4-mercaptopyrrolidine (3.08 g) and diisopropylethylamin (1.09 g) in dry acetonitrile (10.0 ml) was added to the reaction mixture, followed by stirring for 4 hours. The reaction mixture was diluted with ethyl acetate, washed with aqueous potassium phosphate solution and a saturated aqueous sodium chloride solution in order and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-methylpiperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]-hept-2-en-7-one-2-carboxylate.

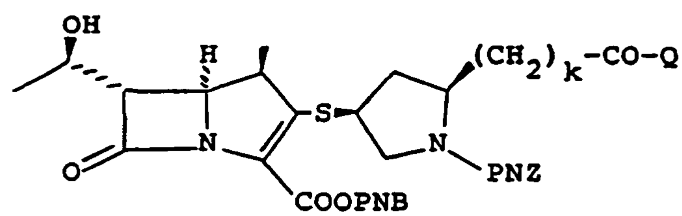
IR_{max} cm^{-1} (neat): 3400, 1750, 1695, 1630, 1593, 1500, 1423, 1390, 1324, 1271, 1193, 1120;

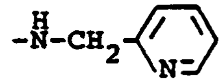
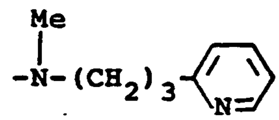
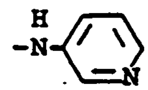
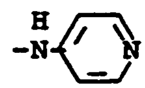
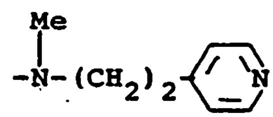
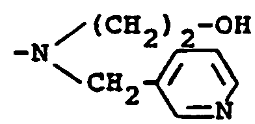
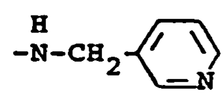
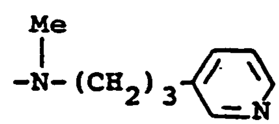
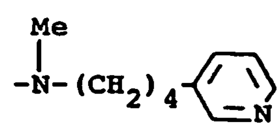
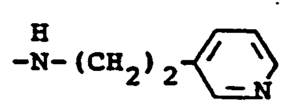
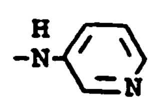
NMR δ ($CDCl_3$): 1.26 (3H, d, J = 7.3 Hz), 1.34 (3H, d, J = 6.3 Hz), 1.91 (1H, m), 2.32 (3H, s), 2.73 (1H, s), 4.72 (1H, m), 5.22 (3H, m), 5.43 (1H, d, J = 13.9 Hz), 7.40 - 7.60 (2H, m), 7.64 (2H, d, J = 8.9 Hz), 8.20 (4H, d, J = 8.9 Hz).

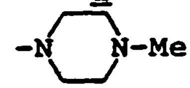
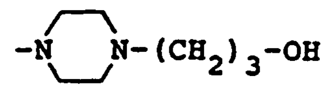
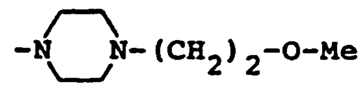
Reference Examples 37 to 50

In the same manner as in Reference Example 36, the compounds as shown in Table 10 were obtained. The physical properties of the compounds obtained follow the Table.

Table 10



Reference Example No.	k	Q
37	0	
38	0	
39	0	
40	0	
41	0	
42	0	
43	0	
44	0	
45	0	
46	1	
47	2	

Reference Example No.	k	Q
48	1	
49	0	
50	0	

Physical properties

Reference Example 37

IR_{max} cm^{-1} (neat):	3370, 1763, 1700, 1602, 1517, 1430, 1398, 1341, 1203, 1130, 1106;
NMR δ ($CDCl_3$):	1.27 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 2.80 (1H, m), 3.28 (1H, dd, J = 3.0 & 6.9 Hz), 3.36 (1H, m), 3.50 (1H, dd, J = 8.0 & 10.9 Hz), 3.71 (1H, m), 4.30 (2H, m), 5.10 - 5.50 (4H, m), 7.10 - 7.70 (6H, m), 7.98 (1H, m), 8.21 (4H, d, J = 8.9 Hz), 8.39 (1H, m).

Reference Example 38

IR_{max} cm^{-1} (neat):	3400, 1761, 1697, 1637, 1515, 1426, 1400, 1340, 1202, 1175, 1132, 1104;
NMR δ ($CDCl_3$):	1.28 (3H, d, J = 6.9 Hz), 1.34 (3H, d, J = 5.6 Hz), 1.88 (3H, m), 2.50 - 2.90 (4H, m), 2.92, 2.97, 3.00, 3.11 (3H as a whole, each s), 3.28 (1H, m), 3.48 (4H, m), 3.69 (1H, m), 3.87 (1H, m), 4.27 (3H, m), 4.75 (1H, m), 5.23 (3H, m), 5.48 (1H, d, J= 13.9 Hz), 7.39 (1H, dd, J = 4.9 & 8.9 Hz), 7.50 (1H, d, J = 8.9 Hz), 8.06 (1H, t, J = 8.9 Hz), 8.18 (4H, d, J = 8.9 Hz), 8.48 (1H, m).

Reference Example 39

IR_{max} cm^{-1} (neat):	3330, 1761, 1710, 1603, 1519, 1420, 1340, 1205;
NMR δ ($CDCl_3$):	1.26 (3H, d, J = 7.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 3.35 (2H, m), 3.84 (1H, m), 4.03 (1H, m), 4.28 (2H, m), 4.56 (1H, m), 5.17 (1H, d, J = 13.6 Hz), 5.30 (2H, s), 5.33 (1H, d, J = 13.6 Hz), 7.60 (2H, d, J = 8.9 Hz), 8.16 (4H, d, J = 8.9 Hz), 8.35 (1H, m), 8.58 (1H, s).

Reference Example 40

IR_{max} cm^{-1} (neat):	3290, 1760, 1702, 1586, 1508, 1397, 1337, 1203,1183;
NMR δ ($CDCl_3$):	1.27 (3H, d, J = 7.2 Hz), 1.35 (3H, d, J = 6.3 Hz), 2.30 (1H, m), 2.64 (1H, m), 3.32 (2H, m), 3.53 (1H, m), 3.83 (1H, m), 4.00 (1H, m), 4.28 (2H, m), 4.55 (1H, m), 5.18 (1H, d, J = 13.8 HZ), 5.25 (2H, m), 5.38 (1H, d, J = 13.8 Hz), 7.47 (2H, m), 7.60 (2H, d, J = 8.6 Hz), 8.17 (2H, d, J = 8.6 Hz), 8.45 (2H, m).

Reference Example 41

IR_{max} cm^{-1} (neat):	3400, 1762, 1698, 1643, 1600, 1517, 1339;
NMR δ ($CDCl_3$):	1.27 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.89, 2.96, 2.98 (3H as a whole, ach s), 5.22 (2H, br. s), 5.25 (1H, d, J = 13.9 Hz), 5.49 (1H d, J = 13.9 Hz), 7.00 - 7.23 (2H, m), 7.40 - 7.58 (2H, m), 7.65 (2H, d, J = 8.6 Hz), 8.21 (4H, m), 8.53 (2H, m).

Ref rence Example 42

IR$_{max}$ cm^{-1} (neat): 3380, 1755, 1693, 1643, 1508, 1337;
NMR δ ($CDCl_3$): 1.27 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 2.03 (1H, m), 2.67 (1H, m), 3.20 - 3.95 (9H, m), 4.05 (1H, m), 4.26 (2H, m), 4.96 (1H, d, J = 13.5 Hz), 5.23 (4H, m), 5.48 (1H, d, J = 13.5 Hz), 7.26 (1H, m), 7.51 (2H, d, J = 8.9 Hz), 7.65 (3H, d, J = 8.6 Hz), 8.22 (4H, m), 8.53 (2H, m).

Reference Example 43

IR$_{max}$ cm^{-1} (KBr): 3350, 1774, 1704, 1656, 1600, 1508, 1423, 1395, 1337, 1315;
NMR δ ($CDCl_3$): 1.24 (3H, m), 1.33 (3H, d, J = 6.3 Hz), 2.47 (1H, m), 2.91 (1H, m), 3.31 (2H, m), 3.54 (1H, dd, J = 5.3 & 11.2 Hz), 3.79 (1H, m), 4.02 (1H, dd, J = 6.0 & 11.2 Hz), 4.20 - 4.60 (5H, m), 5.12 (1H, d, J = 14.2 Hz), 5.20 (2H, br. s), 5.40 (1H, d, J = 14.2 Hz), 7.22 (1H, m), 7.50 (2H, m), 7.60 (2H, d, J = 8.9 Hz), 7.62(1H, m), 8.13 (4H, d, J = 8.9 Hz), 8.45 (1H, m), 8.50(1H, s).

Reference Example 44

IR$_{max}$ cm^{-1} (KBr): 3410, 1768, 1704, 1653, 1603, 1522, 1422, 1403, 1342, 1262;
NMR δ ($CDCl_3$): 1.28 (3H, m), 1.37 (3H d, J = 6.3 Hz), 1.87 (2H, m), 2.70 (3H, m), 2.97, 2.98, 3.09 (3H as a whole, each s), 3.30 - 3.80 (7H, m), 4.78 (2H, m), 5.24 (1H, d, J = 13.8 Hz), 5.30 (2H, br. s), 5.46 (2H, d, J = 13.8 Hz), 7.22 (1H, m), 7.40 (1H, m), 7.50 (2H, d, J = 8.6 Hz), 7.65 (2H, d, J = 8.9 Hz), 8.2 (4H, m), 8.45 (2H, m).

Reference Example 45

IR$_{max}$ cm^{-1} (KBr): 3300, 1773, 1707, 1663, 1604, 1518, 1438, 1402, 1340, 1280, 1265, 1206, 1168, 1147, 1109;
NMR δ ($CDCl_3$): 1.27 (3H, m), 1.37 (3H, d, J = 6.3 Hz), 1.80 - 2.10 (4H, m), 2.67 (2H, m), 2.88, 2.93, 2.95, 3.04 (3H as a whole, each s), 5.20 (2H, br.s), 5.25 (1H, d, J = 13.5 Hz), 5.48 (1H, d, J = 13.5 Hz), 7.23 (1H, m), 7.40 (1H, m), 7.51 (2H, d, J = 8.9 Hz), 7.65 (2H, d, J = 8.3 Hz), 8.12 (4H, d, J = 8.9 Hz), 8.42 (2H, m).

Reference Example 46

IR$_{max}$ cm^{-1} (neat): 3350, 1760, 1696, 1652, 1517, 1419, 1400, 1338, 1196, 1130, 1102;
NMR δ ($CDCl_3$): 1.28 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.0 Hz), 2,82 (2H, m), 5.20 (2H, br. s), 5.23 (1H, d, J = 14.0 Hz), 5.50 (1H, d, J = 14.0 Hz), 7.25 (1H, m), 7.55 (3H, m), 7.66 (2H, d, J = 8.9 Hz), 8.23 (4H, d, J = 8.9 Hz), 8.44 (1H, br.s), 8.48 (1H, d, J = 5.0 Hz).

Reference Example 47

IR$_{max}$ cm^{-1} (neat): 3350, 1760, 1700, 1684, 1598, 1518, 1400, 1336;
NMR δ ($CDCl_3$): 1.27 (3H, d, J = 6.9 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.20 - 2.80 (5H, m), 3.20 - 3.50 (2H, m), 3.28 (1H, dd, J = 2.6 & 6.9 Hz), 3.50 - 3.80 (1H, m), 4.00 - 4.35 (5H, m), 5.37 (2H, ABq, J = 76.9 & 13.9 Hz), 7.53 (2H, d, J = 8.9 Hz), 7.65 (2H, d, J = 8.9 Hz), 8.10 - 8.50 (7H, m), 8.64 (1H, s), 9.09 (1H, br.s).

Reference Example 48

IR$_{max}$ cm^{-1} (neat): 3370, 1760, 1695, 1627, 1517, 1433, 1420, 1398, 1337, 1194, 1132, 1101;
NMR δ ($CDCl_3$): 1.28 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.30 (3H, s), 5.25 (3H,m), 5.50 (1H, d, J = 13.9 Hz), 7.51 (2H, d, J = 8.9 Hz), 7.65 (2H, d, J = 8.9Hz), 8.22 (4H, m).

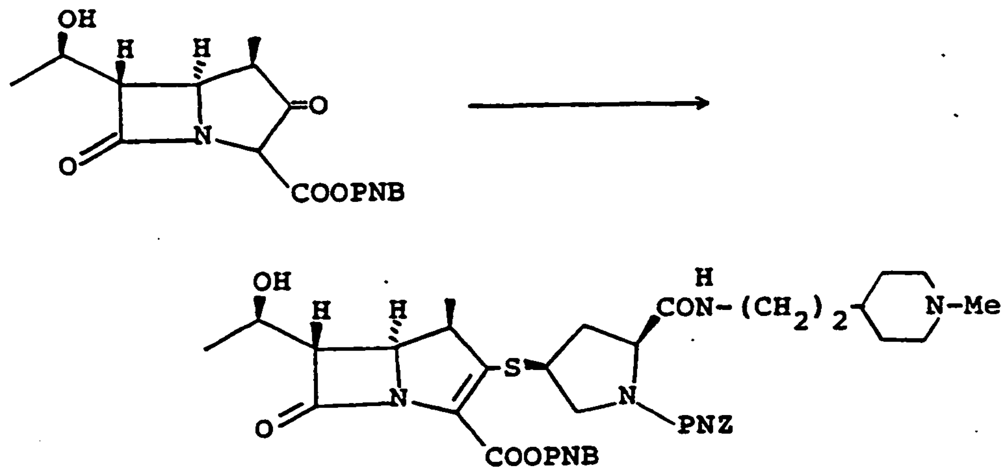
Reference Example 49

IR_{max} cm^{-1} (neat):	3200 (br), 1760, 1700, 1652, 1512, 1336;
NMR δ ($CDCl_3$):	1.28 (3H, m), 1.36 (3H, d, J = 6.3 Hz), 2.02 (3H, m), 2.73 (1H, m), 3.10 (2H, m), 3.24 - 4.80 (18H, m), 5.05 - 5.56 (4H, m), 7.43 (2H x 0.3, d, J = 7.9 Hz), 7.51 (2H x 0.7, d, J = 8.9 Hz), 7.64 (2H, d, J = 8.6 Hz), 8.20 (4H, m).

Reference Example 50

IR_{max} cm^{-1} (neat):	3420 (br), 1763, 1700, 1648, 1602, 1520, 1438, 1243;
NMR δ ($CDCl_3$):	1.26 (3H, m), 1.35 (3H, d, J = 6.3 Hz), 2.92 (1H, m), 2.30 - 2.85 (7H, m), 3.34 (3H x 0.5, s), 3.56 (3H x 0.5, s), 3.20 - 3.83 (9H, m), 4.20 (2H, m), 4.76 (1H, m), 5.08 - 5.55 (4H, m), 7.44 (2H x 0.5, d, J = 8.9 Hz), 7.52 (2H x 0.5, d, J = 8.6 Hz), 7.65 (2H, d, J = 8.9 Hz), 8.20 (4H, m).

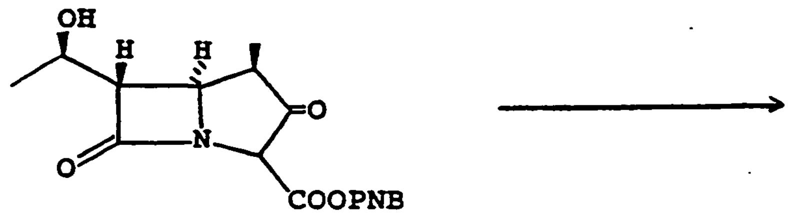
Reference Example 51

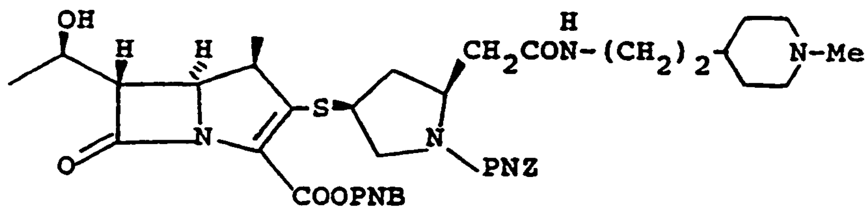


To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (217 mg) in dry acetonitrile (2.0 ml), diisopropylethylamine (93 mg) and diphenyl chlorophosphate (178 mg) were added under ice-cooling, and the resultant mixture was stirred for 3 hours. A solution of (2S,4S)-p-nitrobenzyloxycarbonyl-2-(2-(1-methylpiperizin-4-yl)ethyl)aminocarbonyl-4-mercaptopyrrolidine (293 mg) and 1,8-diazabicyclo[5.4.0]-7-undecene (218 mg) in a mixture of dry acetonitril (2.0 ml) and dry tetrahydrofuran (4.0 ml) was added to the reaction mixture, followed by stirring for 1 hour. The reaction mixture was combined with a phosphate buffer (pH, 7.0) and extracted with dichloromethane 3 times. The organic layer was dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((2-(1-methylpiperizin-4-yl)ethyl)aminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

IR_{max} cm^{-1} (neat):	3300, 1762, 1703, 1519, 1487, 1342, 1204;
NMR δ ($CDCl_3$):	1.24 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 2.35 (3H, br.s).

Reference Example 52



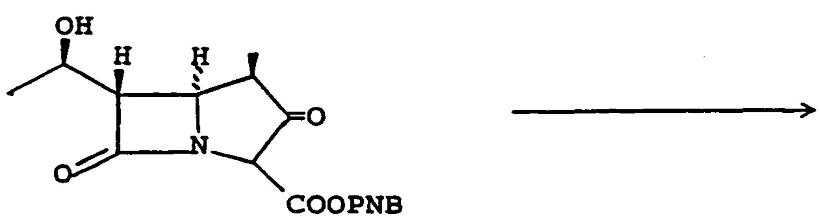


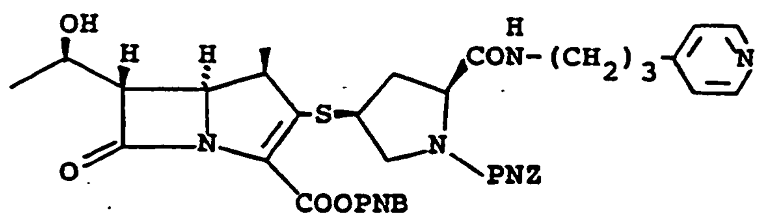
In the same manner as in Reference Example 51, there was obtained (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-[1-p-nitrobenzyloxycarbonyl-2-((2-(1-methylpiperidin-4-yl)ethyl)aminocarbonylmethyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

IR_{max} cm^{-1} (neat): 3350, 1758, 1693, 1518, 1339;

NMR δ ($CDCl_3$): 1.25 (3H, d, J = 7.0 Hz), 1.36 (3H, d, J = 6.3 Hz), 2.35 (3H, br.s).

Reference Example 53





To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (256 mg) in dry acetonitrile (1.5 ml), diisopropylethylamine (108 mg) and diphenyl chlorophosphate (206 mg) were added under ice-cooling, and the resultant mixture was stirred at the same temperature for 4 hours. To a suspension of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-(3-(4-pyridyl)propyl)-aminocarbonyl-4-mercaptopyrrolidine (450 mg) in dry acetonitrile (3.0 ml), bis(trimethylsilyl)acetamide (165 mg) was added, and the mixture was heated to 60° C, followed by allowing to stand. The thus obtained solution was added to the above phosphate solution under cooling with ice, and diisopropylethylamine (108 mg) was add d thereto. After 15 minutes, 1,8-diazabicyclo[5.4.0]-7-undecene (203 mg) was added, followed by stirring for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with aqueous potassium phosphate solution and a saturated aqueous sodium chloride solution in order and dried over anhydrous magnesium sulfat . After removal of the solvent, the residue was dissolved in ethyl acetate (50 ml), 0.1 N hydrochloric acid (5.0 ml) was added while cooling with ice, and the resultant mixture was stirred vigorously.

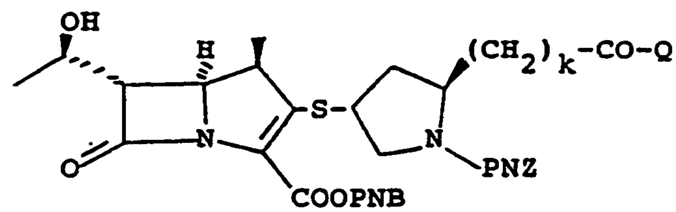
A phosphate buffer (pH, 7.0) was added to the reaction mixture, which was extracted with dichloromethane three times. The extracts were combined together, dried ov r anhydrous magnesium sultate, concentrated and purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-((3-(4-pyridyl)propyl)aminocarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

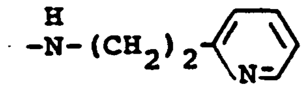
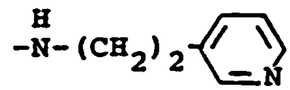
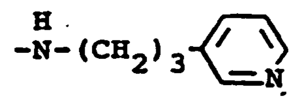
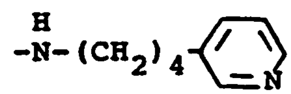
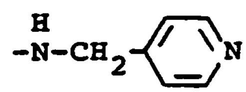
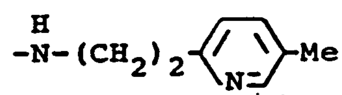
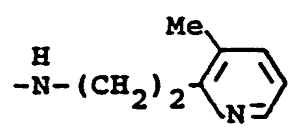
IR_{max} cm^{-1} (neat):	3350, 1760, 1697, 1518, 1340;
NMR δ ($CDCl_3$):	1.26 (3H, d, J = 7.0 Hz), 1.36 (3H, d, J = 6.3 Hz), 1.84 (2H, m), 2.60 (2H, m), 7.09 (2H, m), 7.49 (2H, m), 7.62 (2H, m), 8.20 (4H, m), 8.48 (2H, d, J = 5.9 Hz).

Reference Examples 54 to 60

In the same manner as in Reference Example 53, the compounds as shown in Table 11 were obtained. The physical properties of the compounds obtained follow the Table.

Table 11



Ref rence Example No.	k	Q
54	0	
55	0	
56	0	
57	0	
58	0	
59	0	
60	0	

Physical properties

Reference Example 54

NMR δ ($CDCl_3$): 1.26 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 5.11 (1H, d, J = 13.5 Hz), 5.18 (2H, m), 5.42 (1H, d, J = 13.5 Hz), 7.00 - 7.80 (6H, m), 8.05 (1H, m), 8.19 (4H, d, J = 8.9 Hz), 8.39 (1H, m).

Reference Example 55

IR_{max} cm^{-1} (neat): 3400, 1742, 1680, 1500, 1309, 1251;

NMR δ ($CDCl_3$): 1.27 (3H, d, J = 6.9 Hz), 1.36 (3H, d, J = 6.3 Hz), 1.95 (1H, m), 2.51 (1H, m), 2.84 (2H, m), 3.32 (2H, m), 3.49 (3H, m), 3.73 (1H, m), 3.97 (1H, m), 5.20 (3H, m), 5.42 (1H, d, J = 13.5 Hz), 7.23 (1H, m), 7.51 (3H, m), 7.62 (2H, d, J = 8.6 Hz), 8.18 (4H, d, J = 8.6 Hz), 8.43 (2H, m).

Reference Example 56

IR_{max} cm^{-1} (neat): 3225, 1770, 1703, 1655, 1518, 1422, 1399. 1342, 1318, 1273, 1203, 1166, 1137, 1105;
NMR δ ($CDCl_3$): 1.24 (3H, d, J = 7.3 Hz), 1.35 (3H, d, J = 6.3 Hz), 1.82 (3H, m), 2.61 (2H, m), 3.36 (4H, m), 3.50 (1H, m), 3,76 (1H, m), 4.08 (1H, m), 4.28 (2H, m), 4.38 (1H, m), 5.14 (1H, d, J = 13.9 Hz), 5.24 (2H, br. s), 5.40 (1H, d, J = 13.9 Hz), 7.20 (1H, t, J = 6.0 Hz), 7.48 (3H, br.s), 7.62 (2H, d, J = 8.6 Hz), 8.18 (4H, d, J = 8.3 Hz), 8.42 (2H, br. s).

Reference Example 57

IR_{max} cm^{-1} (neat): 3400, 1767, 1703, 1647, 1520, 1422, 1403, 1343, 1262;
NMR δ ($CDCl_3$): 1.26 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.0 Hz), 2.16 (1H, m), 2.60 (3H, m), 3.27 (5H, m), 3.47 (1H, m), 3.73 (1H, m), 4.02 (1H, m), 4.32 (3H, m), 5.23 (3H, m), 5.46 (1H, d, J = 13.9 Hz), 7.22 (1H, m), 7.46 (3H, m), 7.64 (2H, d, J = 8.9 Hz), 8.21 (4H, d, J = 8.9 Hz); 8.42 (2H, m).

Reference Example 58

NMR δ ($CDCl_3$): 1.27 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.3 Hz), 3.29 (1H, dd, J = 3.0 & 5.9Hz), 5.17 (1H, d, J = 12.9 Hz), 5.23 (2H, br.s), 5.42 (1H, d, J = 12.9 Hz), 7.18 (2H, m), 7.48 (2H, m), 7.63 (2H, d, J = 8.9 Hz), 8.22 (4H, m), 8.51 (2H, m).

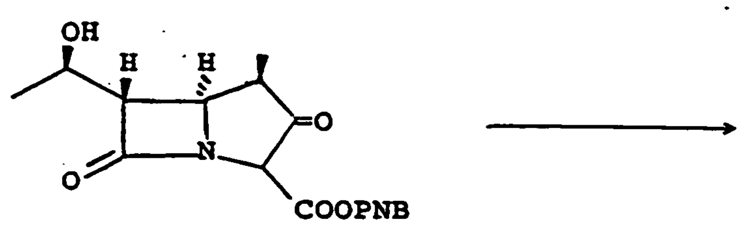
Reference Example 59

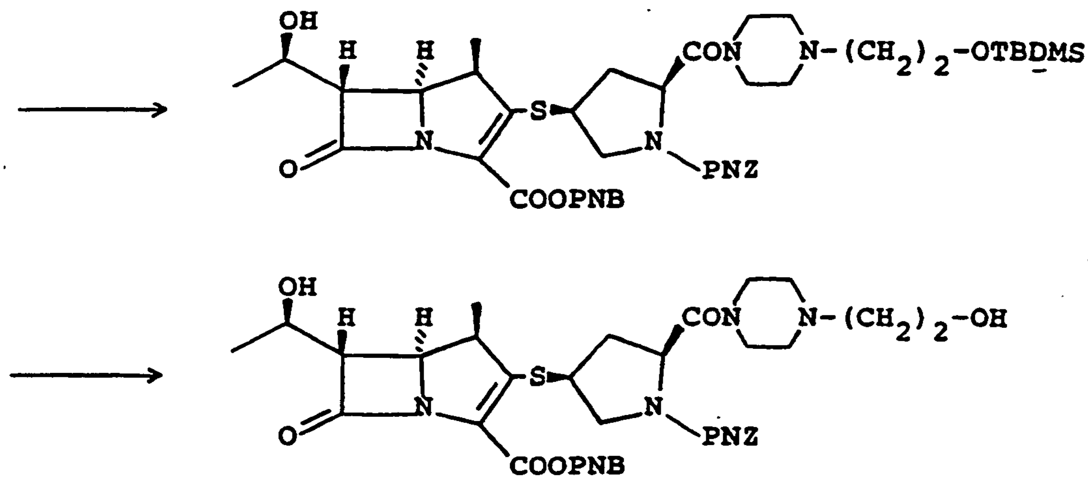
IR_{max} cm^{-1} (neat): 3370, 1756, 1682, 1597, 1510, 1420, 1392, 1335, 1196, 1103;
NMR δ ($CDCl_3$): 1.27 (3H, d, J = 7.3 Hz), 1.34 (3H, d, J = 6.3 Hz), 2.49 (3H, s), 2.78 (2H, m), 3.29 (1H, dd, J = 2.3 & 6.6 Hz), 3.34 (1H, m), 3.49 (2H, m), 3.74 (1H, m), 4.00 (1H, m), 4.27 (2H, m), 4.36 (1H, m), 5.17 (1H, d, J = 13.9 Hz), 5.19 (2H, s), 5.42 (1H, d, J = 13.9 Hz), 7.07 (1H, d, J = 7.9 Hz), 7.44 (3H, m), 7.60 (2H, d, J = 8.9 Hz), 8.16 (4H, d, J = 8.9 Hz), 8.28 (1H, s).

Reference Example 60

IR_{max} cm^{-1} (neat): 3400, 1767, 1703, 1521, 1441, 1399, 1343, 1262, 1203;
NMR δ ($CDCl_3$): 1.24 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.56 (3H, s), 2.84 (2H, m), 3.20 - 3.65 (6H, m), 3.73 (1H, m), 4.08 (1H, m), 4.20 - 4.45 (4H, m), 5.20 (1H, d, J = 13.5 Hz), 5.19 (2H, br. s), 5.45 (1H, d, J = 13.5 Hz), 7.04 (1H, dd, J = 4.9 & 7.6 Hz). 7,43 (1H, d, J = 7.6 Hz), 7.50 (2H, m), 7.63 (2H, d, J = 8.6 Hz), 8.21 (4H, d, J = 8.6 Hz), 8.35 (1H, d, J = 4.9 Hz).

Reference Example 61





a) To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-3,7-dione-2-carboxylate (256 mg) in dry acetonitrile (2.0 ml), diisopropylethylamine (108 mg) and diphenyl chlorophosphate (200 mg) were added under ice-cooling, and the resultant mixture was stirred at the same temperature for 2 hours. A solution of 1-p-nitrobenzyloxycarbonyl-2-(4-(2-(t-butyldimethylsilyloxy)-ethyl)piperazin-2-ylcarbonyl)-4-mercaptopyrrolidine (491 mg) and diisopropylethylamine (108 mg) in dry acetonitrile (2.0 ml) was added thereto, followed by stirring for 2 hours. The reaction mixture was diluted with ethyl acetate, washed with aqueous potassium phosphate solution and a saturated aqueous sodium chloride solution in order and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-(2-(t-butyldimethylsilyloxy)ethyl)piperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

IR_{max} cm^{-1} (neat): 3250, 1763, 1703, 1664, 1657, 1521, 1342;

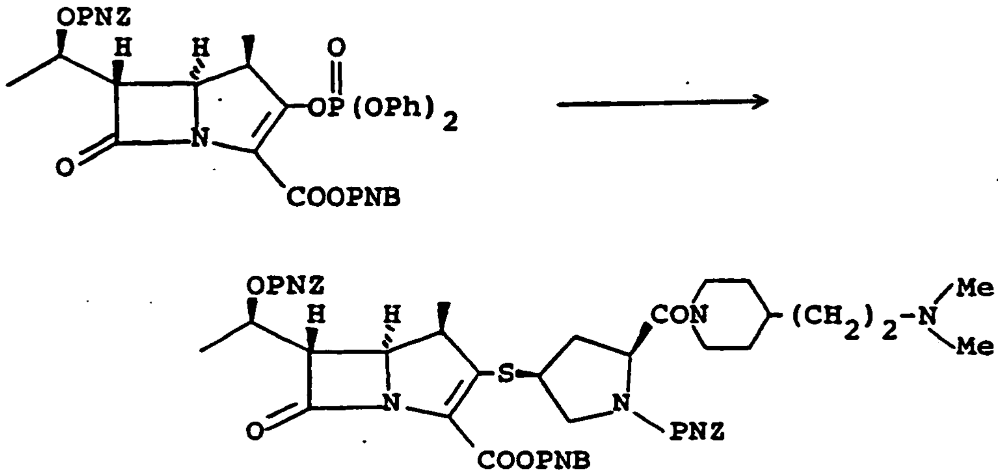
NMR δ ($CDCl_3$): 0.06 (6H, s), 0.89 (9H, s), 1.29 (3H, d, J = 7.3 Hz), 1.37 (3H, d, J = 6.3 Hz), 2.50 (6H, m), 3.38 (2H, m), 3.56 (2H, m), 3.76 (2H, m), 5.10 - 5.55 (4H, m), 7.40 - 7.60 (2H, m), 7.65 (2H, d, J = 8.3 Hz), 8.24 (4H, m).

b) The thus obtained (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-(2-(t-butyldimethylsilyloxy)ethyl)piperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo-[3.2.0]hept-2-en-7-one-2-carboxylate (476 mg) was dissolved in dry tetrahydrofuran (4.0 ml) and stirred at room temperature. Acetic acid (657 mg) and a 1 N tetrahydrofuran solution of tetrabutylammonium fluoride (2.16 ml) were added, and the resultant mixture was stirred at the same temperature for 9 hour. A phosphate buffer (pH, 7.0) was added to the reaction mixture, which was extracted with dichloromethane three times. The organic layer was dried over anhydrous magnesium sulfate, followed by removal of the solvent. The residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyl-3-[1-p-nitrobenzyloxycarbonyl-2-(4-(2-hydroxyethyl)piperazin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-hydroxyethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

IR_{max} cm^{-1} (neat): 3250, 1762, 1703, 1658, 1521, 1342;

NMR δ ($CDCl_3$): 1.28 (3H, d, J = 7.3 Hz), 1.36 (3H, d, J = 6.0 Hz), 1.92 (1H, m), 2.80 (6H, m), 2.93 (1H, m), 3.20 - 3.80 (9H, m), 4.08 (1H, m), 4.26 (3H, m), 4.73 (1H, m), 5.25 (3H, m), 5.49 (1H, d, J = 13.8 Hz), 7.35 - 7.60 (2H, m), 7.64 (2H, d, J = 8.9 Hz), 8.22 (4H, m).

Reference Example 62

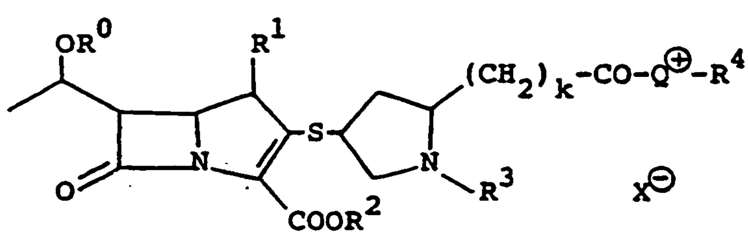


To a solution of (4R,5R,6S,8R)-p-nitrobenzyl-3-(diphenylphosphoryloxy)-4-methyl-6-(1-(p-nitrobenzyloxycarbonyloxy)ethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate (714 mg) in dry acetonitrile (3.0 ml), a solution of (2S,4S)-1-p-nitrobenzyloxycarbonyl-2-(4-(2-dimethylaminoethyl)piperidin-1-ylcarbonyl)-4-mercaptopyrrolidine (505 mg) in dry acetonitrile (3.0 ml) was added under ice-cooling, and 1,8-diazabicyclo[5.4.0]-7-undecene (182 mg) was added thereto, followed by stirring at the same temperature for 2 hours. The reaction mixture was diluted with dichloromethane, washed with a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by silica gel column chromatography to give (4R,5S,6S,8R,2'S,4'S)-p-nitrobenzyloxycarbonyl-3-[1-p-nitrobenzyl-2-(4-(2-dimethylaminoethyl)piperidin-1-ylcarbonyl)pyrrolidin-4-ylthio]-4-methyl-6-(1-(p-nitrobenzyloxycarbonyloxy)ethyl)-1-azabicyclo[3.2.0]hept-2-en-7-one-2-carboxylate.

NMR δ ($CDCl_3$): 1.22 (3H, d, J = 7.3 Hz), 1.29 (3H, d, J = 6.3 Hz), 2.38 (6H, s), 5.00 - 5.50 (6H, m), 7.00 - 7.70 (6H, m), 8.18 (6H, m).

Claims

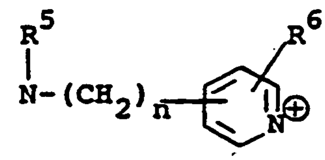
1. A compound of the formula:



(I)

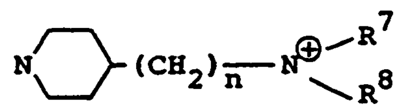
wherein R^0 is a hydrogen atom or a protective group for hydroxyl, R^1 is a lower alkyl group, R^2 is a protective group for carboxyl or a negative charge, R^3 is a hydrogen atom or a protective group for amino, R^4 is a lower alkyl group or a substituted lower alkyl group, k is an integer of 0 to 4, X is an acid residue or an intramolecular COO when R^2 is the negative charge and $Q^{\bullet}$ is a quaternary nitrogen atom-containing group represented by either one of the formulas (1) to (4):

(1)



wherein R^5 is a hydrogen atom, a lower alkyl group or a 2-hydroxyethyl group, R^6 is a hydrogen atom or a lower alkyl group and n is an integer of 0 to 4;

(2)

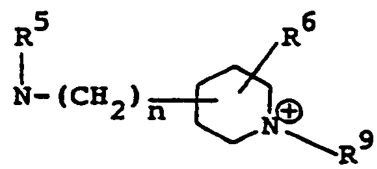


wherein R^7 and R^8 are each a lower alkyl group or may be combined together to form a lower alkylene group, or R^8 represents a subtituted lower alkyl group and n is as defined above;

(3)

wherein R^9 is a lower alkyl group or a substituted lower alkyl group; or

(4)



wherein R^5, R^6, R^9 and n are each as defined above, or its salt.

2. The compound according to claim 1, wherein R^0 and R^3 are each a hydrogen atom, R^2 is a negative charge and X is an intramolecular COO, or its salt.

3. The compound according to claim 2, wherein $Q^{\bullet}$ is a quaternary nitrogen atom-containing group represented by either one of the formulas (1) and (3).

4. The compound according to claim 3, wherein $Q^{\bullet}$ is a quaternary nitrogen atom-containing group represented by the formula (1) wherein R^5 is a hydrogen atom or a methyl group, R^6 is a hydrogen atom and n is is an integer of 0 to 4.

5. The compound according to claim 3, wherein $Q^{\bullet}$ is a quaternary nitrogen atom-containing group represented by the formula (3) wherein R^9 is a methyl group.

6. The compound according to claim 1, wherein R^4 is a C_1-C_5 alkyl group, a C_2-C_5 alkanoyl(C_1-C_5)alkyl group, a carbamoyl(C_1-C_5)alkyl group, a C_1-C_5 alkylaminocarbonyl(C_1-C_5)alkyl group, a di(C_1-C_5)-alkylaminocarbonyl(C_1-C_5)alkyl group or a hydroxy(C_2-C_5)alkyl group.

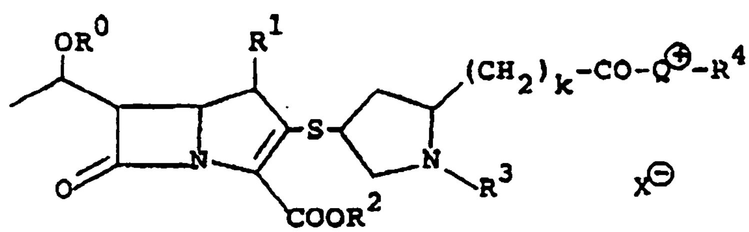
7. The compound according to claim 1, wherein R^1 is a methyl group.

8. The compound according to claim 1, wherein k is zero.

9. The compound according to claim 1, which has a (5S)-configuration.

10. The compound according to claim 1, which has a (4R,5S,6S,8R)-configuraton.

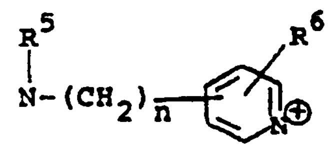
11. A process for producing a compound of the formula:



(I)

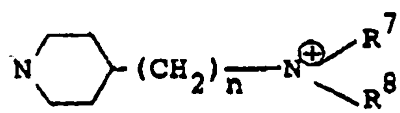
wherein R^0 is a hydrogen atom or a protective group for hydroxyl, R^1 is a lower alkyl group, R^2 is a protective group for carboxyl or a negative charge, R^3 is a hydrogen atom or a protective group for amino, R^4 is a lower alkyl group or a substituted lower alkyl group, k is an integer of 0 to 4, X is an acid residue or an intramolecular COO when R^2 is the negative charge and $Q^{\bullet}$ is a quaternary nitrogen atom-containing group represented by either one of the formulas (1) to (4):

(1)



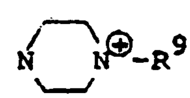
wherein R^5 is a hydrogen atom, a lower alkyl group or a 2-hydroxyethyl group, R^6 is a hydrogen atom or a lower alkyl group and n is an integer of 0 to 4;

(2)



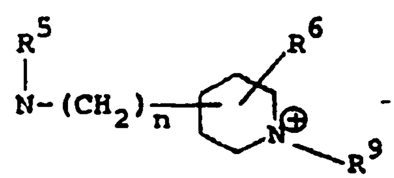
wherein R^7 and R^8 are each a lower alkyl group or may be combined together to form a lower alkylene group, or R^8 represents a subtituted lower alkyl group and n is as defined above;

(3)

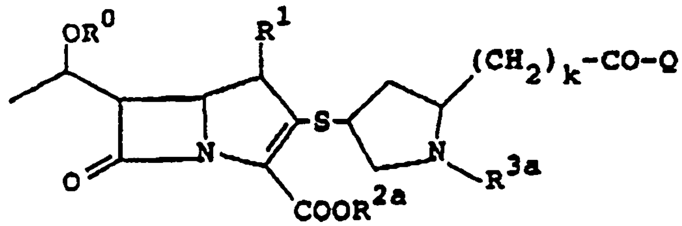


wherein R^9 is a lower alkyl group or a substituted lower alkyl group; or

(4)



wherein R^5, R^6, R^9 and n are each as defined above,
or its salt, which comprises reacting a compound of the formula:

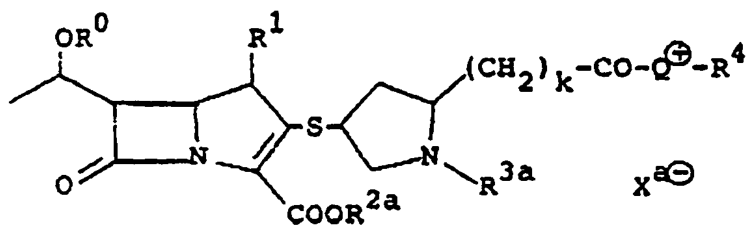


(II)

wherein R^0, R^1 and k are each as defined above, R^{2a} is a protective group for carboxyl, R^{3a} is a protective group for amino and Q is a tertiary nitrogen atom-containing group resulting from elimination of a positive charge from either one of the groups (1) to (4) represented by $Q^\oplus$ with a compound of the formula:

R^4-X^a (III)

wherein R^4 is as defined above and X^a is an acid residue to give a compound of the formula:



(IV)

wherein R^0, R^1, R^{2a}, R^{3a}, R^4, k, $Q^\oplus$ and X^a are each as defined above, optionally followed by subjecting the latter to reaction for elimination of the hydroxyl-protecting group represented by R^0, the carboxyl-protecting group represented by R^{2a} and/or the amino-protecting group represented by R^{3a}, thereby giving the compound (I) wherein R^0 and R^3 are each a hydrogen atom and R^2 is a negative charge.

12. A pharmaceutical composition which comprises as an active ingredient a pharmaceutically effective amount of at least one of the compounds as claimed in any preceding claim, and at least one pharmaceutically acceptable inert carrier or diluent.

13. Use of a compound according to claim 1 as an antimicrobial agent.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 10 2101

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	EP-A-0 243 686 (SUMITOMO) * Claims *	1,7-13	C 07 D 477/00 A 61 K 31/40
Y	EP-A-0 182 213 (SUMITOMO) * Claims *	1,7-13	
A	EP-A-0 126 587 (SUMITOMO) * Claims *	1,7-13	
A	EP-A-0 242 134 (MERCK) * Claims *	1,12,13	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D 477/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	18 April 91	CHOULY J.

CATEGORY OF CITED DOCUMENTS

- X: particularly relevant if taken alone
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